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EXPERIENCE WITH THE "ANOXEMIA TEST" IN PATIENTS WITH ANGINA PECTORIS AND IN THOSE WITH ATYPICAL CHEST PAIN

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SINCE the interpretation of pain in the precordial region is often difficult, great advance would be achieved if a means were available for separating by objective criteria those instances which are of cardiac origin, especially those which represent "angina pectoris." Physical examination, x-ray photographs of the heart, and electrocardiograms cannot be interpreted in terms of functional capacity, and the therapeutic test with nitroglycerin is not always specific.

Twenty-five per cent of White's[1] patients with a history of angina did not show any abnormality of the heart by the usual methods of examination. Biorck[2] states that in only about one-sixth of his series of one hundred fifty patients with suspected angina was the diagnosis reasonably certain. With increasing longevity, more people suffer from either organic or functional heart disease. Insurance benefits are dependent in many instances on the cardiac status of the individual. An estimate of the functional capacity of the coronary circulation would be of importance when major surgical procedures are contemplated. These are some of the reasons for a definite diagnostic implement which gives objective data about coronary sufficiency. The anoxemia test has been used in this direction.

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LITERATURE

In 1921, Green and Gilbert,[3] using a rebreathing apparatus to induce a gradually progressive anoxemia, showed that lack of an adequate oxygen supply produced changes in the form of the electrocardiogram. Katz and co-workers[4] and Rothschild and Kissin[5] made similar observations. In 1938, Larsen[6] reported his experience with anoxemia in 133 subjects. His subjects breathed a mixture containing only 9 per cent oxygen for six to eight minutes. He found that there was no constant relationship between the occurrence of pain and electrocardiographic alterations. He also pointed out that the absence of an abnormal response does not rule out "stenotic lesions" of the coronary vessels. In 1933, Dietrich and Schwiegk[7] found abnormal features in the electrocardiogram which followed breathing air deficient in oxygen.

Levy and associates have made extensive observations which have resulted in establishing the method and standardizing the criteria for the anoxemia test as it is now used. They have demonstrated sufficient correlations to indicate that alterations in the form of the electrocardiogram caused by induced anoxemia can be used to estimate the functional efficiency of the coronary circulation. In 1938, Levy and associates[8] described the apparatus and method now employed in the anoxemia test, but used 12 per cent oxygen and 88 per cent nitrogen instead of the 10 per cent oxygen and 90 per cent nitrogen gas mixture now generally employed. Observations were made on thirty-seven subjects with cardiac disease and on eleven with normal hearts. During the test, the oxygen saturation in the arterial blood ranged from 67 to 83 per cent. They came to the conclusions that "there was no constant relationship between the occurrence of cardiac pain and changes in heart rate, respiratory rate, blood pressure, venous pressure, circulation time, and the degree of arterial unsaturation. Pain occurred inconstantly in repeated tests, except in two patients with aortic stenosis and in one with advanced coronary lesions."

These results prompted further studies by Levy, Bruenn, and Russell[9] who standardized the procedure as a test for coronary insufficiency. Using the same apparatus and 10 per cent oxygen and 90 per cent nitrogen, changes in the form of the electrocardiogram which followed the induction of anoxemia in 105 persons were analyzed to establish criteria for normal and abnormal responses. In 1940, Levy and associates[10] studied the actions of certain drugs (aminophylline, nitrites, digitalis) in modifying the effects of induced anoxemia in patients with coronary insufficiency. In 1941, Levy and associates[11] published the results of 326 tests carried out on 262 subjects. They obtained a positive test in 18 per cent of thirty-three patients with suspected coronary sclerosis, in 31 per cent of twenty-two patients with coronary sclerosis but no history of angina, and in 55 per cent of seventy-three patients with coronary sclerosis and a history of anginal attacks. On the basis of these studies they made the criteria for determining normal and abnormal response more rigid.

In 1942, Patterson and co-workers[12] studied 157 cases of coronary sclerosis with the anoxemia test and obtained positive electrocardiographic tests in 49 per cent and pain in another 20 per cent as presumptive evidence of coronary

insufficiency. They again pointed out, as they had earlier,[13] that the occurrence of pain during the first ten minutes of a negative electrocardiographic test is of particular importance, since in a follow-up study of fourteen such cases, four showed a positive electrocardiographic test, one suffered a coronary occlusion, and two patients died of cardiac disease. They observed at this time that their fourth criterion for a positive test, namely, "partial reversal in the direction of the T wave in Lead IVF, accompanied by an RS-T deviation of 1.0 mm. or more in this lead,"[12] occurred in normal subjects and in patients with coronary sclerosis at about equal frequency. Therefore, they discontinued the use of this criterion.

In 1941, Burnett and associates[14] used the Levy method to study 125 subjects in Colorado whose history, physical and electrocardiographic examinations, and response to exercise were normal; they were considered normal by all usual clinical standards. They found in 19.2 per cent an electrocardiographic response which, according to Levy's criteria, was indicative of coronary artery insufficiency. In their conclusion they state, "that there is some correlation between the efficiency of the coronary circulation and the electrocardiographic response seems apparent, but we have encountered 'abnormal' responses in normal subjects and 'normal' responses in abnormal subjects too frequently to justify, in our opinion, the use of this test as it is at present employed in clinical diagnosis." Patterson and associates[12] state that the differences found by Burnett and co-workers[14] were presumably due to difference in altitude, slight differences in technique, and the use of cases which were not carefully selected.

In 1943, Nylin[15] obtained 22 per cent positive tests in 163 private patients with typical or suspected angina pectoris.

In 1945, Pruitt and co-workers[16] reported a study of the anoxia test in 289 cases, using the method of Levy. They obtained seventy-one electrocardiographically positive tests in 282 of the cases with clinical evidence of angina pectoris. Of the ninety-two cases in which the history was suggestive of angina pectoris, the test was positive in 53.2 per cent. An additional 19.6 per cent experienced pain, but showed a negative test electrocardiographically. In 23.9 per cent of the cases, the test was completely negative. In 108 cases with an equivocal history, the test was electrocardiographically positive in 19.5 per cent, and in an additional 18.5 per cent of the cases, there was pain without significant changes of the electrocardiogram. In 50 per cent of the cases the test was negative.

In 1946, Biorck[2] reviewed his experience with the anoxemia test and compared it with that of Larsen (1938), Levy (1945), and Pruitt, Burchell, and Barnes (1945). He found that the test was positive in about 20 per cent of those patients "moderately suspected" of having angina. He found this figure surprisingly constant in three series of observations reported in the literature. In his own series, it was positive in 18 per cent of 100 patients without a "coronary electrocardiogram" at rest. Between 30 and 50 per cent of patients with "probable or certain coronary disease" will show a positive test. He concluded that a negative test does not exclude the existence of coronary disease.

We have been using the anoxemia test, as described by Levy and his associates, for the past five and one-half years and now add our observations to the expanding experience with this procedure.

MATERIAL AND METHOD

Our experience is based upon the results of 138 tests performed on 119 patients. The ages of the patients in all groups ranged from 20 to 77 years, the average age being 38 years. We divided our subjects into four groups.

Group I was composed of twenty-six patients who were used as controls and in whom no evidence of heart disease could be elicited. These were studied in order to gain facility with the test before using cardiac patients and also to ascertain for ourselves what the effects were in normal subjects. Their ages ranged from 20 to 57 years; there were twenty-three men and three women.

Group II included five patients, four women and one man, the youngest being 23 years and the oldest, 39 years of age: two had dextrocardia and the test was performed on them to see what effect anoxemia might have. In two patients who suffered from hypertension, the test was used to test the coronary efficiency before sympathectomy. The fifth subject was a 23-year-old Negro woman with active primary syphilis.

Group III was composed of forty patients classified as having "typical angina." There were thirty-six men and four women, the youngest being 35 and the eldest, 66 years of age. We wished to see what the results were in patients who suffered from clinically typical angina, and how close the objective correlation was in this group. The pain was typical with respect to onset, distribution, and the effect of rest, cold, emotion, and nitroglycerin; in six of these there was a previous history of coronary occlusion.

Group IV is designated as the "atypical pain" group. It was composed of forty-eight subjects who experienced vague pain in the chest or arm. In them the diagnosis of hiatus hernia, scalenus anticus syndrome, cervical rib, gall bladder disease, and neurocirculatory asthenia had to be considered. They were referred to us for clinical appraisal of the pain and with inquiry as to whether we could secure objective evidence of diminished coronary reserve. Of the forty-eight subjects, thirty-nine were men and nine were women, the youngest being 28 and the oldest, 77 years of age.

In seven subjects the test was repeated several times. Four had positive tests on all occasions, two had one positive and one negative test each, and one had a negative test on both occasions. In all of these cases, only the test with the most marked change was recorded for the analysis. The effect of the administration of aminophylline orally and intravenously was observed in two patients.

The apparatus and procedure followed were those described by Levy and associates.[11] The system consists of a tank containing 10 per cent oxygen and 90 per cent nitrogen gas which is allowed to flow at a rate approximately that of normal pulmonary ventilation. The gas mixture first flows through a humidifier, then into a rubber bag which is kept full, but not distended. The mixture

TABLE I. COMPARISON OF THE RESULTS OF THE ANOXEMIA TEST IN PATIENTS WITH TYPICAL ANGINA AND IN THOSE WITH ATYPICAL PAIN

	TYPICAL ANGINA GROUP	"ATYPICAL PAIN" GROUP
Number of tests in same number of patients	40	48
Abnormal resting electrocardiogram	11	10
Normal resting electrocardiogram	29	38
Postive anoxemia test	18 (45%)	6 (13%)
Pain during text	25 (63%)	13 (27%)
Pain during first ten minutes	15 (38%)	8 (17%)
Positive anoxemia or pain	29 (73%)	19 (40%)
Positive anoxemia or pain in ten minutes	26 (65%)	14 (29%)
Both positive anoxemia and pain	14 (35%)	0 (0%)
Pain only	11 (28%)	13 (27%)
Abnormal electrocardiogram with positive anoxemia	5 (45%)	3 (30%)
Normal electrocardiogram with positive anoxemia	13 (45%)	3 (8%)
Abnormal electrocardiogram with pain	8 (73%)	2 (20%)
Normal electrocardiogram with pain	17 (59%)	11 (29%)
Neither positive anoxemia nor pain	11 (28%)	29 (60%)
Neither positive anoxemia nor pain in ten minutes	14 (35%)	34 (71%)

The occurrence of a positive anoxemia test in a patient with typical angina in whom the test confirmed the clinical diagnosis is illustrated by Case 1.

CASE 1.—G. K. (History No. 399691), a Greek restaurant worker, 51 years of age, gave a history of oppressive precordial pain of two years' duration. The family history revealed no evidence of cardiovascular disease. He had been a waiter and labor organizer since coming to this country at the age of 19 years. He smoked one to two packages of cigarettes a day and used alcoholic beverages only occasionally.

The first attack of precordial pain had occurred two years earlier during a labor argument. Since then he had continued to have typical anginal pain which had increased in severity and frequency. At first it was relieved by nitroglycerin, but more recently it had been uninfluenced by the drug. The attacks were typically related to exertion and emotion and, to a less extent, to overeating. The pain was pressing and squeezing in character and was localized to the precordial area. It was not possible to decide whether he had had a myocardial infarction early in the course of his present illness.

The patient was extremely emotional, excitable, and dramatic in his expressions. The ocular fundi showed moderate arteriolar thickening. The heart was not enlarged on physical examination or in the x-ray photographs of the chest (by the method of Ungerleider and Gubner).[17] The point of maximum impulse was in the sixth intercostal space, 8.0 cm. to the left of the midsternal line. There was a normal sinus mechanism and the rate was 74 per minute. The first and second heart sounds were clear and there were no murmurs. The blood pressure was 120/75. The resting electrocardiogram was essentially normal; the anoxemia test was positive (Fig. 1).

The occurrence of a positive anoxemia test in a patient with typical angina complicated by traction diverticulum of the esophagus, in whom the test aided in differentiation of the chest pain and confirmed the clinical impression was illustrated by Case 2.

CASE 2.—B. C. (History No. 417897), a Jewish painter, 58 years of age, had had attacks of substernal pain for six years. The pain, which was squeezing in character and without radiation, was at first of great intensity and localized to the substernal region, but for the past two years it had been of less intensity. The pain had usually come on with exertion and after walking one to two blocks and could be relieved immediately by nitroglycerin. He seldom had the pain while painting, but did no climbing or strenuous lifting.

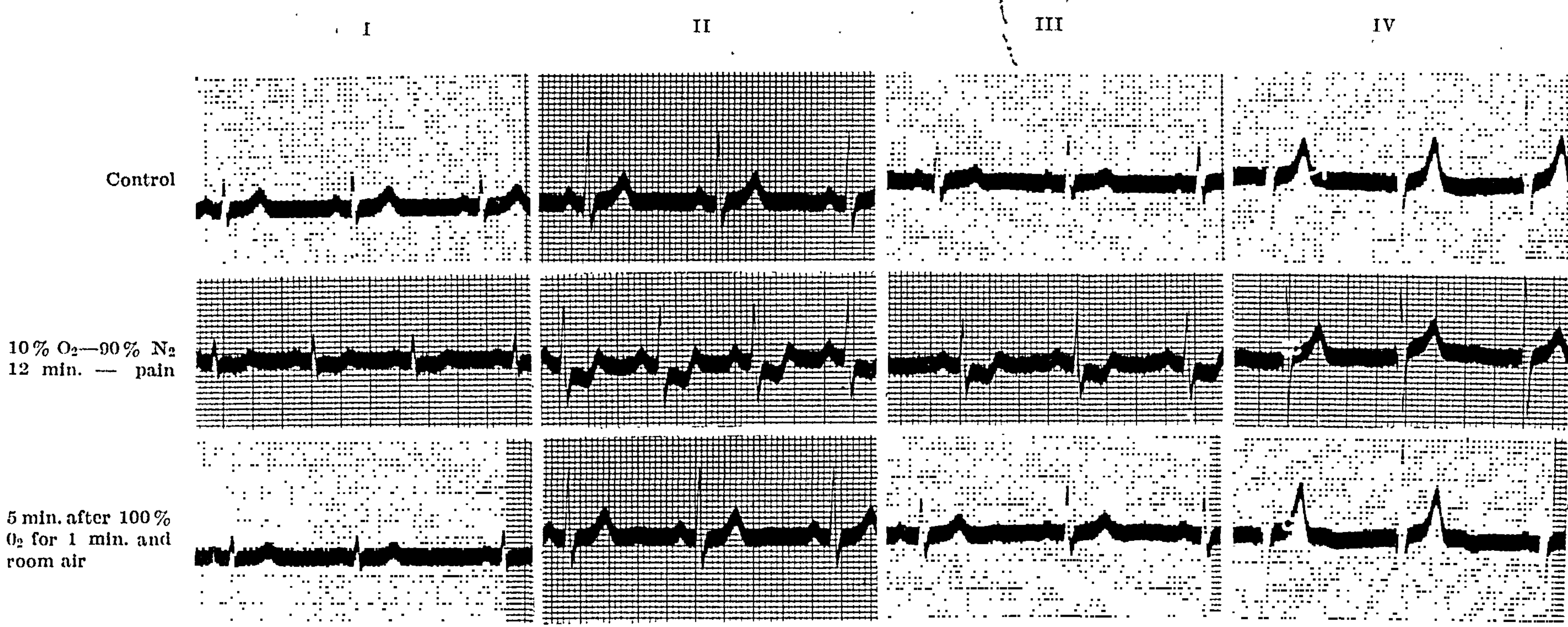

Fig. 1.—In this figure are reproduced the pertinent electrocardiograms of Case 1, G. K., in whom the anoxemia test was positive (see text). The standardization was such that 1.0 cm. deflection of the string represented 1.0 millivolt.

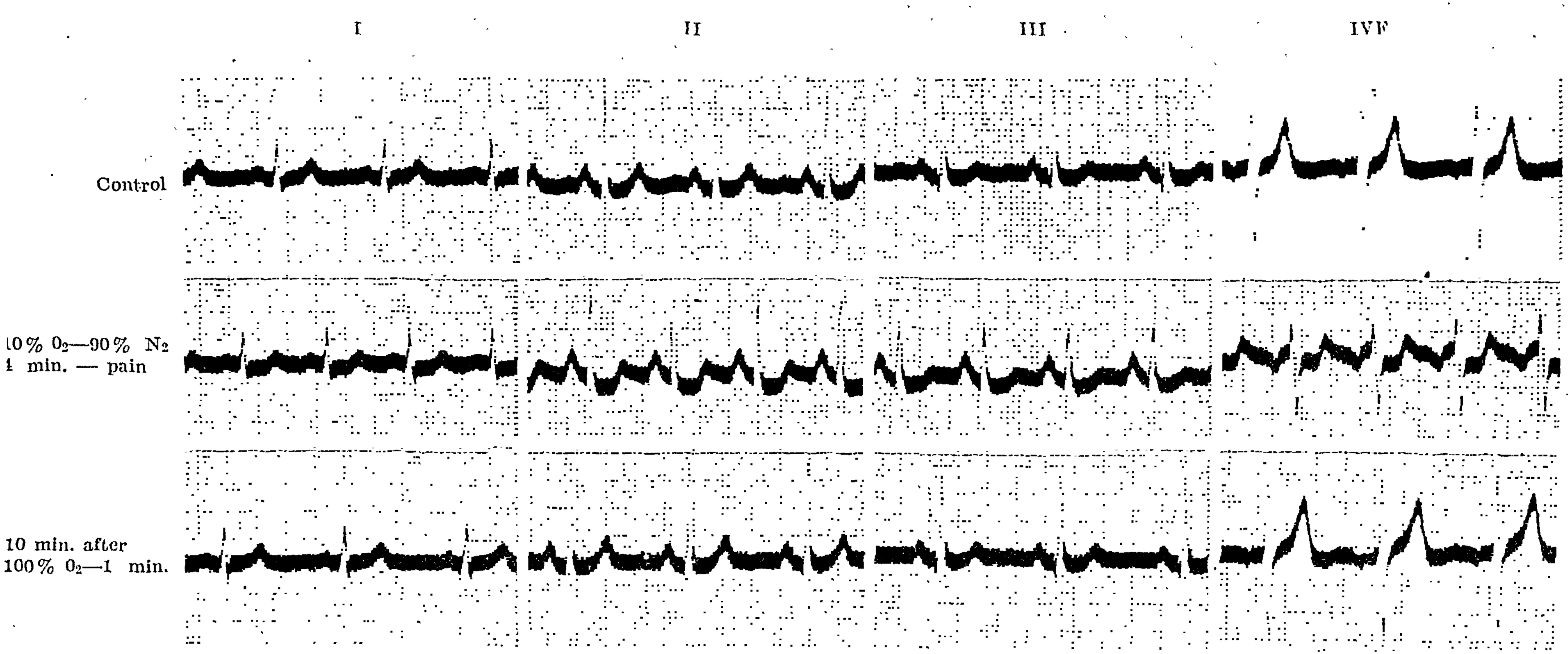

Fig. 2.—In this figure are reproduced the salient electrocardiograms of Case 2, B. C., in whom the anoxemia test was positive (see text).

He was small and thin. Funduscopic examination showed no arteriolar changes. The lungs were clear. The heart was not enlarged by physical examination or x-ray mensuration. The heart sounds were of good quality and there were no murmurs. The blood pressure was 110/70. The resting electrocardiogram was normal.

His case was of particular interest because the diagnosis of coronary sclerosis with coronary insufficiency was made when he was first seen in July, 1945, and in August, 1945, he was admitted to the Surgical Service because of regurgitation of food and a squeezing sensation in the chest after eating. X-ray study of the gastrointestinal tract revealed a traction diverticulum of the middle third of the esophagus. However, in spite of this finding, his pain was still considered typical of angina pectoris, and an anoxemia test was carried out. In four minutes pain appeared which was similar to the pain experienced on exertion, and electrocardiographic changes sufficient to indicate a positive test developed (Fig. 2).

Case 3 illustrated the occurrence of a positive anoxemia test in a subject with atypical pain in whom the test aided in establishing a diagnosis of coronary insufficiency.

CASE 3.—M. F. (History No. 425148), a 54-year-old former social worker who was referred from the Psychosomatic Clinic because of pain over the left breast of two to three years' duration. The pain had an aching quality and lasted up to five minutes at a time; it was not related to exertion, excitement, or eating. Nitroglycerin had been tried, but gave no relief. Occasionally, she had had pain in the shoulders.

She appeared to be nervous and excited. Her heart was not enlarged on physical examination or in the x-ray photographs of the chest. The heart sounds were of normal intensity. Normal sinus rhythm prevailed and there was a soft blowing systolic murmur over the apex of the heart. The blood pressure was 160/90. The resting electrocardiogram was essentially normal.

This patient was of particular interest because of various emotional problems for which she was being followed in the Psychosomatic Clinic. It was difficult to evaluate clearly her pain which was clouded by many and varied complaints. Electrocardiographic changes during the anoxemia test (Fig. 3) were of sufficient magnitude to indicate a positive response.

Effect of Hypertension on the Test.—The results of the test were compared in patients with hypertension with those having normal blood pressures in the groups with typical angina and atypical pain (Table II). Hypertension was

TABLE II. EFFECT OF HYPERTENSION ON THE ANOXEMIA TEST

	TYPICAL ANGINA		ATYPICAL PAIN	
	PATIENTS WITH HYPER-TENSION	PATIENTS WITH NORMAL BLOOD PRESSURE	PATIENTS WITH HYPER-TENSION	PATIENTS WITH NORMAL BLOOD PRESSURE
Patients in each group	11 (28%)	29 (72%)	10 (20%)	38 (80%)
Abnormal resting electrocardiogram	2 (18%)	9 (31%)	4 (40%)	6 (16%)
Normal resting electrocardiogram	9 (82%)	20 (69%)	6 (60%)	32 (84%)
Positive anoxemia test	3 (27%)	15 (52%)	3 (30%)	3 (8%)
Pain during test	7 (64%)	18 (62%)	0	13 (34%)
Pain during first 10 minutes	4 (36%)	11 (38%)	0	8 (21%)
Positive anoxemia or pain	7 (64%)	22 (76%)	3 (30%)	17 (45%)
Positive anoxemia or pain in 10 minutes	6 (55%)	20 (69%)	3 (30%)	11 (29%)
Both positive anoxemia and pain	3 (27%)	11 (38%)	0	0
Pain only	4 (36%)	7 (24%)	0	13 (34%)
Total number of patients	40		48	

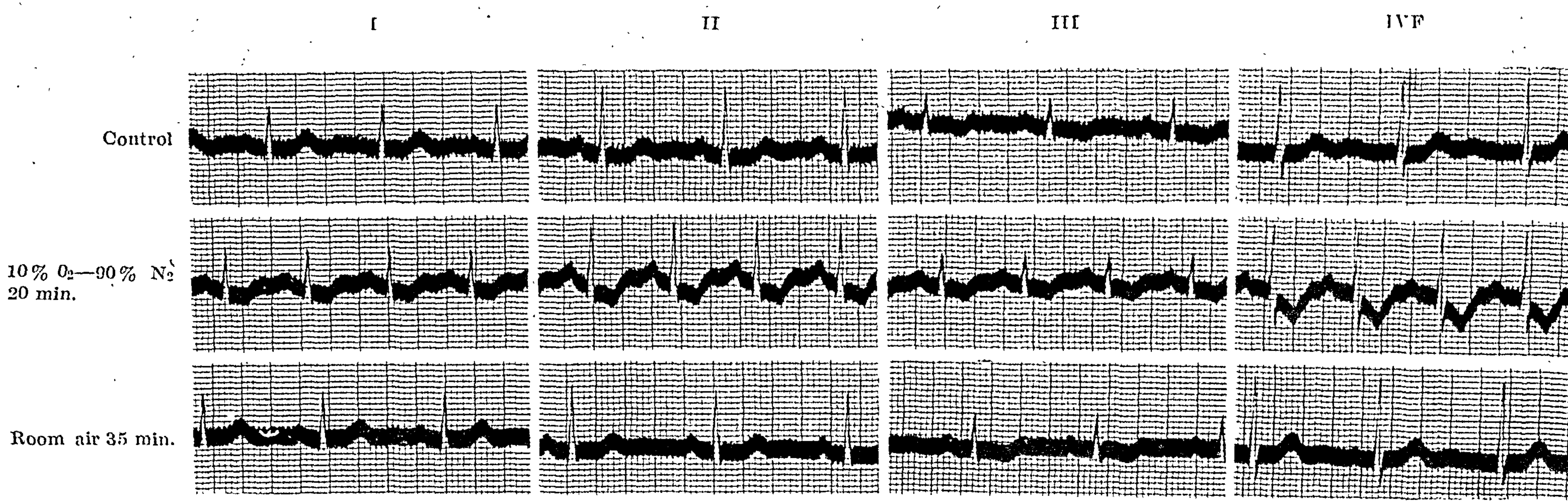

Fig. 3.—In this figure are reproduced the significant electrocardiograms of Case 3, M. F., in whom the anoxemia test was positive (see text).

considered to be present if the systolic pressure was above 140 and the diastolic above 90 mm. of mercury.

In the group with typical pain there were more patients with normal blood pressure than with hypertension. The electrocardiogram was more frequently abnormal in those without hypertension than in those with it. The anoxemia test was positive twice as frequently in those with normal blood pressure as in those with hypertension (52 compared with 27 per cent). The occurrence of pain was essentially the same in both.

In the group with atypical pain, the electrocardiogram was more frequently abnormal in the hypertensive patients than in those with normal blood pressure. The anoxemia test was positive in 30 per cent of those with hypertension and in 8 per cent of those with normal blood pressure; the incidence was essentially the same in hypertensive patients with atypical pain as in hypertensive patients who had typical angina.

It appears, therefore, that in patients with typical angina the presence of hypertension does not increase the likelihood of obtaining a positive test, but makes it less likely; in atypical pain the reverse is true, namely, that hypertension increases the frequency of a positive test. In short, the presence of hypertension adds one more factor suggesting a cardiac origin of the discomfort in these patients.

Effect of Heart Size on the Anoxemia Test.—When x-ray photographs of the chest were available, the heart sizes of the subjects were estimated both by the method of Ungerleider and Gubner[17] and by the cardio-thoracic ratio; the estimation of size made on physical examination was used in those subjects not having x-ray photographs of the chest. Eleven subjects in the group with typical angina and ten in the group with atypical pain had enlarged hearts (Table III). Three patients in each group had abnormal resting electrocardiograms.

Positive anoxemia tests occurred more frequently in those without cardiac enlargement than in those with large hearts in the group with typical pain, while the reverse was the case in those with atypical pain. In short, the enlarged heart in patients with atypical pain gives one more reason to suggest a cardiac origin of the discomfort.

Effect of Both Cardiac Enlargement and Hypertension on the Anoxemia Test.—The results of the anoxemia test in patients with both hypertension and enlarged hearts in the groups with typical angina and atypical pain were also appraised (Table IV). Again, in the typical group the anoxemia test was found to be positive more frequently in those with hearts of normal size and normal blood pressure than in those with enlarged hearts and hypertension (48 compared with 29 per cent). The occurrence of pain was essentially the same in both.

In the group with atypical pain, the incidence of positive anoxemia tests in those with hypertension and enlarged hearts was much greater than in the subjects with hearts of normal size and with normal blood pressures (50 compared with 9 per cent). It is of interest that pain did not occur in any of the subjects with both cardiac enlargement and hypertension.

TABLE III. EFFECT OF CARDIAC ENLARGEMENT ON THE ANOXEMIA TEST

	TYPICAL ANGINA		ATYPICAL PAIN	
	PATIENTS WITH ENLARGED HEARTS	PATIENTS WITH HEARTS OF NORMAL SIZE	PATIENTS WITH ENLARGED HEARTS	PATIENTS WITH HEARTS OF NORMAL SIZE
Patients in each group	11	29	10	38
Abnormal resting electrocardiogram	3	8	3	7
Normal resting electrocardiogram	8	21	7	31
Positive anoxemia	4 (36%)	14 (48%)	2 (20%)	4 (11%)
Pain during test	6 (55%)	19 (66%)	3 (30%)	10 (26%)
Pain during first 10 minutes	4 (36%)	11 (38%)	1 (10%)	7 (18%)
Positive anoxemia or pain	6 (55%)	23 (79%)	5 (50%)	14 (37%)
Positive anoxemia or pain in 10 minutes	6 (55%)	20 (68%)	3 (30%)	11 (29%)
Abnormal ECG with positive anoxemia	1 (33%)	4 (50%)	1 (33%)	2 (29%)
Normal ECG with positive anoxemia	3 (38%)	10 (48%)	1 (14%)	2 (6%)
Abnormal ECG with pain	2 (66%)	6 (66%)	0	2 (29%)
Normal ECG with pain	5 (62%)	12 (57%)	3 (43%)	8 (26%)
Neither positive anoxemia nor pain	5 (45%)	6 (21%)	5 (50%)	24 (63%)
Neither positive anoxemia nor pain in 10 minutes	5 (45%)	9 (32%)	7 (70%)	27 (71%)
Total number of patients	40		48	

TABLE IV. THE EFFECT OF BOTH CARDIAC ENLARGEMENT AND HYPERTENSION ON THE ANOXEMIA TEST

	TYPICAL ANGINA		ATYPICAL PAIN	
	PATIENTS WITH BOTH	PATIENTS WITH NEITHER	PATIENTS WITH BOTH	PATIENTS WITH NEITHER
Patients in each group	7	33	4	44
Abnormal resting electrocardiogram	2	9	1	9
Normal resting electrocardiogram	5	24	3	35
Positive anoxemia	2 (29%)	16 (48%)	2 (50%)	4 (9%)
Pain during test	4 (57%)	21 (64%)	0	13 (30%)
Pain during first 10 minutes	2 (29%)	13 (39%)	0	8 (18%)
Positive anoxemia or pain	4 (57%)	25 (76%)	2 (50%)	17 (39%)
Positive anoxemia or pain in 10 minutes	4 (57%)	22 (67%)	2 (50%)	12 (27%)
Abnormal ECG with positive anoxemia	0	5 (56%)	0	3 (33%)
Normal ECG with positive anoxemia	2 (40%)	11 (46%)	2 (67%)	1 (3%)
Abnormal ECG with pain	1 (50%)	7 (78%)	0	2 (22%)
Normal ECG with pain	3 (60%)	14 (58%)	0	11 (31%)
Neither positive anoxemia nor pain	3 (43%)	8 (24%)	2 (50%)	27 (61%)
Neither positive anoxemia nor pain in 10 minutes	3 (43%)	11 (33%)	2 (50%)	32 (73%)
Total number of patients	40		48	

Results of the Anoxemia Test in Patients Who Had Sustained Previous Coronary Occlusions.—There were six patients in whom the history, examination, and electrocardiograms indicated that coronary occlusions had occurred at

some time in the past (Table V). Four (67 per cent) had a positive test or pain, while two (33 per cent) showed neither. The test was positive electrocardiographically less frequently in these subjects (33 per cent) than in the whole group of patients with typical angina (45 per cent).

TABLE V. RESULTS OF THE ANOXEMIA TEST IN PATIENTS WITH PREVIOUS CORONARY OCCLUSIONS

Patients with previous coronary occlusions	6
Positive anoxemia	2 (33%)
Negative anoxemia	4 (67%)
Pain during test	4 (67%)
Pain during first 10 minutes	2 (33%)
Positive anoxemia or pain	4 (67%)
Positive anoxemia or pain in 10 minutes	3 (50%)
Neither positive anoxemia nor pain	2 (33%)

Changes in RS-T Segments and T Waves.—None of the subjects in the control group showed total RS-T deviation of more than 3.0 mm., and in the majority the deviation was no more than 0.9 millimeter (Fig. 4). In the atypical group, however, there was a greater depression of the RS-T segments; six subjects showed an RS-T deflection greater than 3.0 millimeters. In the typical group, sixteen patients had deviations greater than 3.0 mm., while in twenty-four, deviations were less than this. This corresponds closely to the results of Patterson and co-workers.[12]

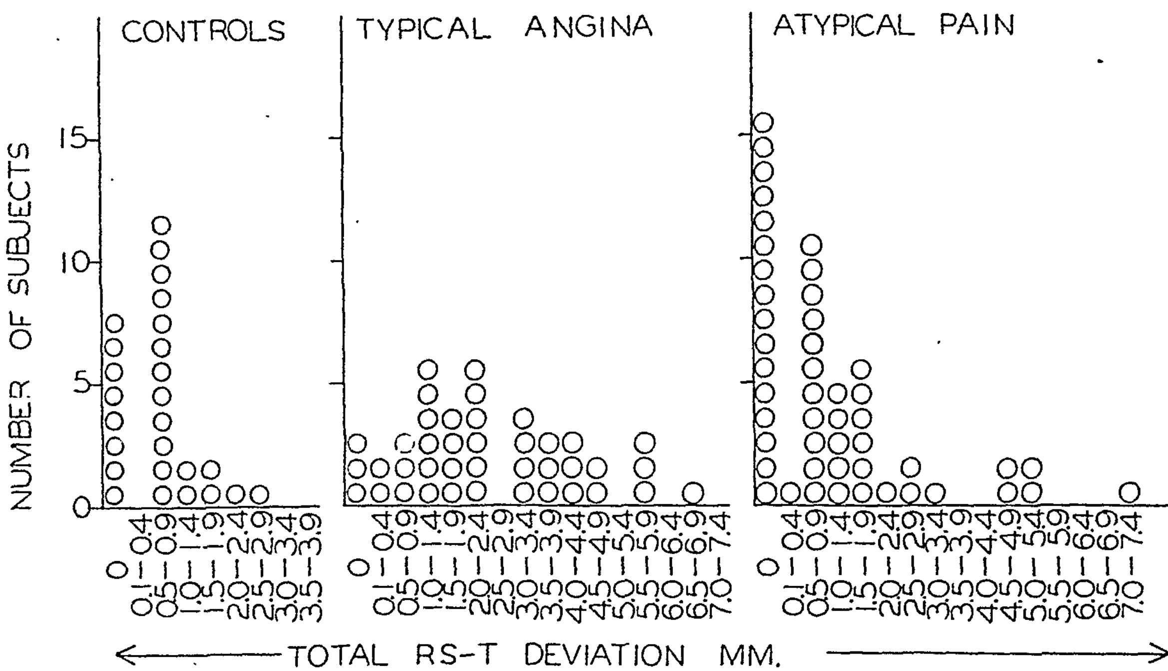

Fig. 4.—In this figure are shown scatter diagrams of the total RS-T deviations in millimeters during the anoxemia test in the control group and in the groups with typical angina and with atypical pain.

There was partial reversal of the T wave in thirteen of the subjects with typical angina. This occurred nine times in Leads I and II, eight times in Lead IV F, and only twice in Lead III among these thirteen subjects. Six subjects with atypical pain had partial reversal of the T wave: once in Lead I, three times in Lead II, and twice in both Leads III and IV F. One subject each in the control and miscellaneous group had partial reversal of the T wave; this was in Lead IV F in both cases. Complete reversal of the T wave occurred in two subjects in the miscellaneous group; twice in Lead II and once in both Leads III and IV F. Complete reversal of the T wave in Lead I occurred in one subject in the group with typical angina. In the group with atypical pain, there was complete reversal of T waves in three subjects: once in both Leads I and II and twice in Lead IV F. None of the patients in the control group had complete reversal of the T wave.

Reactions to the Test.—The most common effect of the test was the appearance of slight to marked cyanosis of the lips, ear lobes, face, or nailbeds. This occurred in over 80 per cent of the subjects. Twenty subjects had a slight headache or feeling of "fullness or pounding of the head." Seventeen subjects complained of slight dizziness. Seven subjects became nauseated and two vomited. The other reactions in order of frequency were faintness, drowsiness, tingling or numbness of fingers, fatigue, numbness of arms, choking sensation in the throat, and a heavy feeling in the chest. These symptoms occurred alone or in various combinations. Two subjects had mild hysterical reactions which prevented the test from being completed.

One patient had a vasovagal reaction during which the blood pressure fell from 260/130 to 160/90. There were no ill effects from this sharp drop in the blood pressure and the blood pressure returned to its previous level on the administration of oxygen. Another patient, a known epileptic, had a petit mal seizure which lasted approximately two minutes. His electrocardiogram during the seizure showed frequent ventricular premature contractions, but no other significant changes were found. He recovered promptly following the administration of 100 per cent oxygen. We have adhered rigidly to Levy's technique and precautions in using the test.

Correlation of the Anoxemia Test With the Exercise Tolerance Test.—Twenty-one patients had the exercise tolerance test with electrocardiograms as well as the anoxemia test. The test was carried out in the morning before breakfast or in the afternoon, if the patient had not eaten lunch. We carried out the test as follows: The patient rested lying down for one-half hour in the Heart Station. A control electrocardiogram with chest lead was then taken. The patient then walked over two steps at his own pace until he experienced discomfort, dyspnea, or fatigue. He lay down at once and a second electrocardiogram was taken. A third one was taken after an interval of twenty minutes. The control electrocardiogram was examined and compared with previous records made before the patient exercised. Whenever marked depressions of the RS-T segments or partial or complete reversal of the T waves or both resulted from exercise, the test was considered positive. There were ten subjects with typical angina,

nine with atypical pain, and two in the miscellaneous group (Table VI). In patients with typical angina, there appeared to be a close parallel between the two tests. Seventy per cent of the subjects in the typical group had a positive exercise test as evidence of coronary insufficiency compared with 45 per cent who were electrocardiographically positive in the anoxia test, or compared with 65 per cent when pain in ten minutes was included. The anoxemia test detected one positive reaction when the exercise test was negative. On the other hand, the exercise test was positive in two subjects in whom the anoxemia test was negative. One of these subjects was known to have coronary artery disease, since he had suffered coronary occlusion in the past.

TABLE VI. COMPARISON OF THE RESULTS OF EXERCISE TOLERANCE AND ANOXEMIA TESTS IN THE SAME PATIENT

	TYPICAL ANGINA	ATYPICAL PAIN	MISCELLANEOUS
Exercise tests performed	10	9	2
Positive exercise tests	7 (70%)	1 (13%)	0
Negative exercise tests	3 (30%)	8 (87%)	2 (100%)
Positive exercise tests with positive anoxemia	5	1	0
Negative exercise tests with positive anoxemia	1	0	0
Positive exercise tests with negative anoxemia	2	0	0
Negative exercise tests with negative anoxemia	2	8	2

The exercise test was positive in only one of nine patients with atypical pain, and in this subject the anoxemia test was also positive. In the other eight subjects, both the exercise and anoxemia tests were negative. Two subjects in the miscellaneous group had both negative exercise and anoxemia tests.

Effect of Aminophylline on the Anoxemia Test in Patients With Coronary Insufficiency.—The effect of aminophylline was tested in two subjects who had coronary sclerosis and positive anoxemia tests, one of whom has since died of coronary occlusion with myocardial infarction.

The first patient, J. McG. (History No. 306719), a 53-year-old white man, on Jan. 20, 1942, was found to have a positive anoxemia test with RS-T depression of 5 mm. (Fig. 5) and decrease in amplitude and inversion of the T waves in Leads I, II, III, and IVF, but no subjective symptoms of coronary insufficiency. On March 10, 1942, the anoxemia test was repeated with essentially the same results as before, the total depression of the RS-T segments being 5.5 mm.; the T waves decreased in amplitude a total of 25 mm. and became inverted in all leads.

On March 1, 1942, the subject was given aminophylline, 0.24 Gm. intravenously, and an anoxemia test performed thirty-five minutes after the injection. The RS-T segments now were only depressed 3.75 mm. and the T waves decreased in amplitude only 14.5 mm.; however, there was still partial to complete inversion of the T waves in all leads.

The patient was then placed on aminophylline, 0.2 Gm. orally, four times daily, and the anoxemia test was repeated on March 21, 1942. There were observed essentially the same changes that followed the intravenous administration of 0.24 Gm. of aminophylline, the RS-T segments being depressed 4.0 mm. and the T waves decreased in amplitude 15 mm.; yet these changes were not as marked as when the patient was receiving no medication.

He continued to take 0.2 Gm. of aminophylline four times a day orally, and on March 25, 1942, the anoxemia test was repeated, this time with the addition of 0.24 Gm. of aminophylline, intravenously, ten minutes before the test. There were occasional auricular premature contractions following the aminophylline, and the anoxemia produced a depression of the RS-T segments of only 2.5 mm. and decrease in the amplitude of the T waves of 14 millimeters.

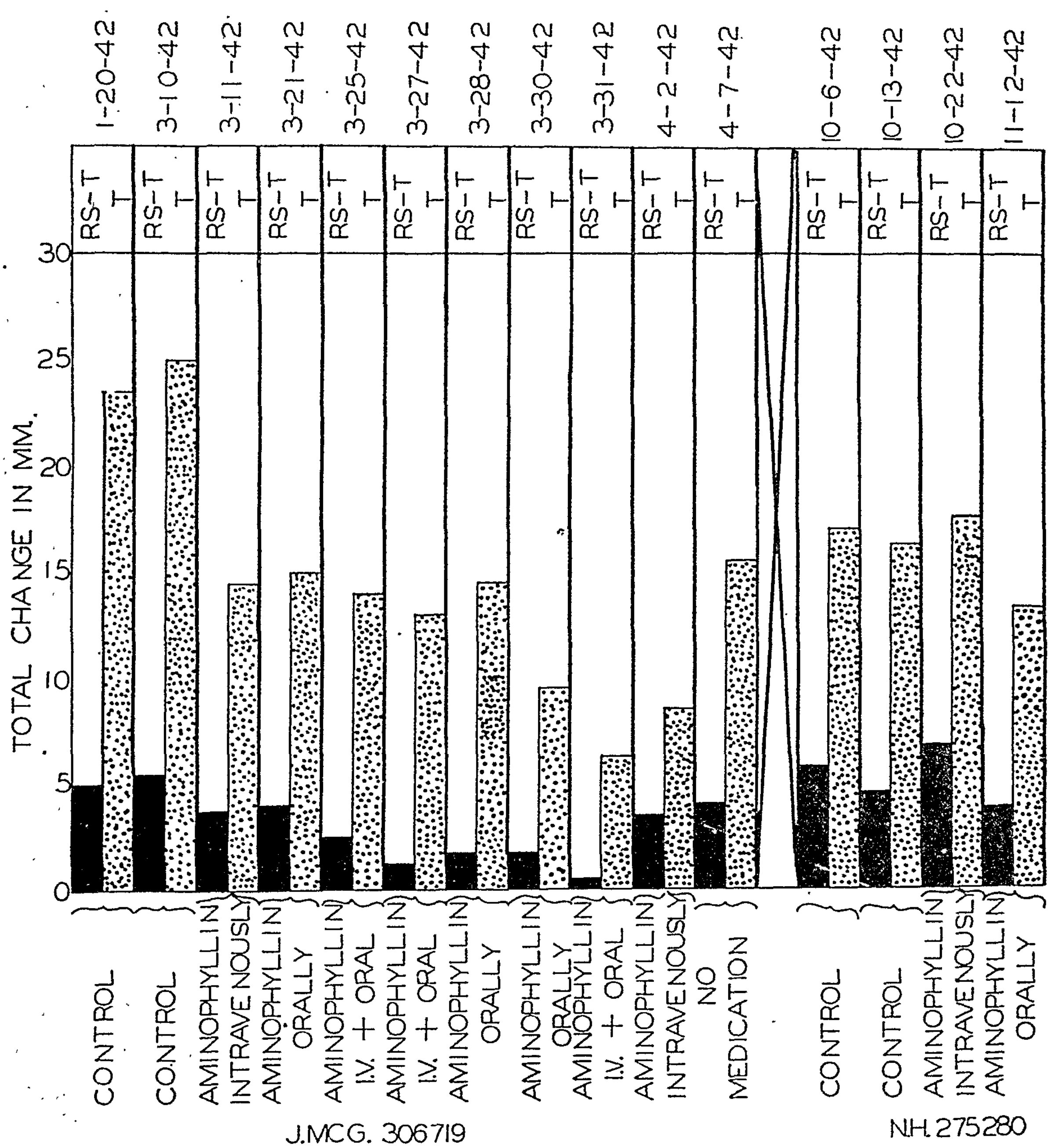

Fig. 5.—In this figure are shown the RS-T deviations and T-wave changes during the anoxemia test when patients J. McG. and N. H. were given aminophylline by mouth and intravenously (see text).

He was then placed on 0.2 Gm. of aminophylline every day. On March 27, 1942, the test was again performed, this time fifteen minutes following the intravenous injection of 0.24 Gm. of aminophylline. There was further lessening of the depression of the RS-T segments (1.25 mm.) and the T waves decreased in amplitude 13 millimeters.

On March 28, 1942, the test was again performed with the patient now on a regular oral dosage of 0.2 Gm. of aminophylline four times a day with an additional 0.4 Gm. given orally two hours prior to the test. This continued to maintain the depression of the RS-T segments at the minimum level of 1.75 mm. and the T waves decreased in amplitude 14.5 millimeters.

With the subject still on this medication, the test was performed two days later, one hour after he had received orally 0.2 Gm. of aminophylline. He continued to have an RS-T depression of only 1.75 mm., and the T waves decreased in amplitude 9.5 mm. with inversion of T_1 and T_4 only.

On March 31, 1942, with the subject on 0.2 Gm. of aminophylline four times a day, and fifteen minutes following intravenous injection of 0.24 Gm. of aminophylline the anoxia now produced a depression of the RS-T segment of 0.5 mm. and the T waves decreased in amplitude only 6.25 millimeters.

The oral administration of aminophylline was discontinued and on April 2, 1942, the test was repeated five minutes after aminophylline, 0.24 Gm., was administered intravenously. The RS-T segments now became more depressed (3.5 mm.); however, the T waves only decreased in amplitude 8.5 millimeters. The subject was given no further medication, and on April 7, 1942, the anoxemia test was again repeated. The RS-T depression of 4.0 mm. and decrease in T waves of 15.5 mm. now indicated a response approaching that observed during the control period before aminophylline was tried.

Aminophylline, in a dose of 0.24 Gm., injected intravenously, diminished the RS-T deviation 32 per cent. With the addition of 0.2 Gm. of aminophylline, administered orally four times a day, the RS-T deviation was reduced 90 per cent in the course of two weeks. The T waves were also markedly modified. These results suggest that the drug exerted a beneficial action in improving coronary circulation.

The second subject, N. H. (History No. 275880), 51 years of age, had his first anoxemia test on Oct. 6, 1942. This test showed a total depression of the RS-T segments of 5.75 mm. and changes in T waves of 17 mm. (Fig. 5). There was partial inversion of T_1 and T_4 and complete inversion of T_2. He had no subjective symptoms during the test. On Oct. 13, 1942, the anoxemia was repeated for control before aminophylline was administered. There were essentially the same changes as before, the RS-T segments being depressed 4.5 mm. and the changes in T waves being 16.25 mm., largely in the negative direction.

On Oct. 22, 1942, after a control electrocardiogram had been made, aminophylline, 0.24 Gm., was given intravenously. No significant changes were observed in records taken five and ten minutes after the injection; the anoxemia test caused no essential changes in the T waves and less marked depression of the RS-T segments as compared with the two previous tests.

After the patient had taken 0.1 Gm. of aminophylline orally four times a day for three weeks, another anoxemia test was performed on Nov. 12, 1942. There was still rather marked depression of the RS-T segments of 3.75 mm. and decrease im amplitude of the T waves in Leads I, II, III, and IVF of 13.25 mm. with partial to complete reversal of the T waves in Leads I, II, and IVF. The patient had no subjective symptoms of coronary insufficiency. These results indicate that aminophylline by mouth had a slight effect on improving the coronary circulation.

Follow-up.—As far as we have been able to learn, only one subject in the series has expired. His anoxemia test was positive. He died five years after the test was made. On post-mortem examination, a recent myocardial infarction was found. None of the subjects with negative anoxemia tests have died. Two patients with positive anoxemia tests and one with a negative anoxemia test have had posterior rhizotomy performed because of intractable anginal pain. All have done well to date, the earliest operation having been done six years ago.

Two subjects with hypertension, one with a positive anoxemia test and the other with a negative test, have had bilateral thoracolumbar sympathectomies. Two years later the lowering of blood pressure was maintained. Another subject with a negative anoxemia test and atypical pain had developed electrocardiographic changes like those seen after anterior myocardial infarction but had no clinical symptoms of coronary occlusion, and is doing well.

DISCUSSION

From these observations it is apparent that a large number of the patients who suffered from clinically typical angina pectoris exhibited significant electrocardiographic changes when exposed to low concentration of oxygen, indicating a correlation between typical angina and these objective findings; in the presence of electrocardiographic changes with anoxemia, the inference is suggested that impairment in the coronary circulation is present. On the other hand, in normal subjects during anoxia, electrocardiographic changes were insignificant. Between these two groups, namely the group of normal subjects and the group with typical angina, was a group of patients with atypical pain, in some of whom the pain may have been due to angina. In a small number of this group the electrocardiographic changes under anoxemia were significant. This experience is similar to the already published experience of other observers.[2,6,11,16] The incidence of positive tests in the group with typical angina is slightly higher than the over-all incidence in the "probable or certain coronary" cases collected by Biorck,[2] in which the range was from 30 to 50 per cent. This can probably be attributed to our selection of the cases for the typical group so that it was made up of patients about whom there could be no doubt clinically that they had angina. This selection was purposeful in order to see how close the correlation of clinical impression and the objective test was. The fact that the incidence of positive electrocardiographic tests was lower in our group with atypical pain (13 per cent) than in Biorck's[2] group of "moderately suspected cases of coronary disease" (20 per cent) was due to the placing in our group of patients referred with an inquiry concerning the nature of pain which, in many instances, was not cardiac in origin.

The use of pain induced under anoxemia as evidence of decreased coronary reserve is the cause of some concern and reflection, since one is using an induced subjective symptom which might be no more reliable than the patient's history of pain. Levy and associates,[13] however, state, "we were struck by the fact that in patients with coronary sclerosis who experienced pain during the test, even though no significant changes appeared in the electrocardiograms, the cardiac lesions were often progressive." "Of a group of fourteen subjects showing a negative reaction with pain, 28.6 per cent later had a positive reaction and 21.4 per cent had complications or died of heart disease." In a later report, Patterson and co-workers[12] state that, "the occurrence of pain, even in the absence of significant electrocardiographic changes, affords presumptive evidence of a diminished coronary reserve. Its appearance during the first ten minutes of a negative test is of particular importance." On the other hand, Pruitt and co-workers[16] state that "the occurrence of pain unattended by significant electrocardiographic changes during a test does not impress us as an event likely to contribute significantly to the solution of a diagnostic problem."

There was an appreciable difference in incidence of pain in our typical and atypical groups, 63 per cent of the former developing pain during the test as opposed to 27 per cent of the latter; 38 per cent of the typical group had pain during the first ten minutes in comparison with only 17 per cent of the atypical

group. It is apparent that if induced pain were a reliable indicator it would enhance the usefulness of the test.

The ultimate development of a positive electrocardiographic test and other evidence of heart disease in patients who originally showed only pain during the test lends weight to the argument of Levy and associates[13] concerning the importance of pain. We have not had occasion to observe this progression in our series. The occurrence of pain in the atypical group in the absence of other objective evidence of coronary insufficiency (electrocardiographic changes during anoxemia) suggests that anoxemia may lower the threshold for pain or induce types of pain other than that associated with coronary artery disease. Although pain is a subjective reaction and may be an unreliable indicator of coronary insufficiency, it seems, from the type of pain which in the majority of the typical cases appeared real and resembled the anginal pains and from the observations of Levy and his co-workers, that the development of pain during the anoxemia test should be considered, with certain limitations, as strong presumptive evidence of coronary insufficiency.

In our series, patients who had sustained previous coronary occlusions had positive electrocardiographic tests less frequently than the whole group with typical angina (33 per cent compared with 45 per cent). This indicates that patients with coronary occlusions may regain sufficient collateral circulation during the period of healing and afterward show no defect within the limits of this test as carried out. We might have expected a higher incidence of positive tests in this group if this had not been the case. This is in general agreement with the findings of Levy and associates[11] who reported two cases. One of the patients had a negative anoxemia test three years after a coronary occlusion, later died of peritonitis and pneumonia, and was found, on post-mortem examination, to have healed infarcts involving the left ventricle and interventricular septum. The other patient had a clinical picture typical of coronary occlusion and electrocardiographic changes of posterior infarction. Five months later he had a positive anoxemia test which became negative three months later still.

The results of the anoxemia tests in patients with hypertension and with enlarged hearts are of interest. In the group with typical pain, the anoxemia test was positive twice as frequently in those with normal blood pressure as in those with hypertension. On the other hand, in the group with atypical pain, the test was positive in 8 per cent of those with normal blood pressure and in 30 per cent of those with hypertension. Moreover, the test was positive more frequently in the group with typical pain in those with normal sized hearts then in those with large hearts; the reverse was the case in those patients with atypical pain. The findings were similar to those just described when the results of the anoxemia test in patients with both hypertension and enlarged hearts were compared in the group with typical angina and the group with atypical pain. It appears, therefore, in the group with atypical pain that pain in patients with hypertension or cardiac enlargement, or both, is more likely to be associated with the heart than in the group with typical angina. We have no explanation to offer for these findings.

In twenty-one patients, we were able to compare the results of the anoxemia test with those of the exercise tolerance test. The two tests are not comparable in the kind of stress to which the heart muscle is subjected by way of coronary circulation. The tests may be used to supplement each other, since either may occasionally be positive when the other is negative. In patients in the typical angina group who received both tests, the exercise tolerance test was positive more frequently than was the anoxemia test. These results are in agreement with those of Evans and Bourne.[18] The anoxemia test, however, has the following advantages over the exercise tolerance test: (1) A number of patients suffering from intermittent claudication, arthritis, or advanced age are unable to climb steps; in these, the anoxemia test only can be used. (2) We are of the opinion that the anoxemia test is safer and more easily controlled. (3) The anoxemia test can be used to study the effect of various drugs on the coronary circulation. (4) In the step test there is a lapse of time following the exercise and the taking of the electrocardiogram during which the electrocardiogram may begin reversion to its control configuration. (5) The exercise test is not without the danger of the induction of acute heart failure, while in the anoxemia test the subject is at rest and, as an added safety measure, he is attached to a closed system in which 100 per cent oxygen can be given immediately.

In one patient, the use of aminophylline decreased markedly the electrocardiographic changes induced by anoxemia. In another patient, the effect was less marked. These results are in agreement with the observations of Williams and associates.[19] These results have been interpreted as giving evidence that this drug increased the coronary circulation, presumably by coronary dilatation.

All investigators are agreed that the positive electrocardiographic test is evidence of diminished coronary reserve. Basis for this view is strengthened as evidence is collected from the analysis of the data of patients with positive tests who have later suffered coronary occlusion and from the autopsy examination of those who have died. With respect to this, one of our patients who had a positive anoxemia test died five years later and at autopsy was found to have had a myocardial infarct. Biorck[2] has collected the following data from the observation of Levy and his associates and from his own data: (1) Six patients with positive anoxemia tests and five with negative tests but anginal pain died suddenly, presumably of heart disease; (2) two subjects with positive tests had post-mortem evidence of coronary sclerosis, four with abnormal electrocardiograms and negative tests had marked coronary sclerosis, and three subjects with normal electrocardiograms and negative tests had slight coronary sclerosis or none at all. A still larger autopsy series is needed before more definite conclusions can be drawn.

The variability in response to the anoxemia test is no doubt due to several factors: (1) Although the concentration of oxygen breathed is 10 per cent, all patients do not experience the same level of anoxemia, and, therefore, the blood reaching the coronary circulation is not of uniform oxygen saturation in all patients. (2) Even if the same saturation were obtained, the caliber of the vessels in each patient would determine the flow to the heart muscle.

SUMMARY

1. It should be emphasized again that the presence of a normal electrocardiogram does not rule out angina pectoris.

2. Using the apparatus and technique described by Levy and associates, anoxemia tests were carried out on twenty-six normal subjects, forty patients suffering from typical angina pectoris, forty-six patients with "atypical pain," and six other subjects.

3. In none of the twenty-six normal subjects was a positive electrocardiographic response recorded.

4. The anoxemia test gave electrocardiographic evidence of coronary insufficiency in 45 per cent of the group with typical angina, compared with 13 per cent of the group with atypical pain.

5. When pain was included, the test gave evidence of coronary insufficiency in 73 per cent of the group with angina, and in only 40 per cent of the group with atypical pain.

6. Although only 13 per cent of the atypical cases had positive electrocardiographic changes with anoxemia, 27 per cent experienced pain, which was approximately the same as the pain in those with typical angina; this suggests the possibility that pain of an origin other than coronary disease may be aggravated by anoxemia.

7. In 32 per cent of the patients with symptomatically and therapeutically typical angina pectoris, this test failed to elicit changes under the prevailing conditions, and in 71 per cent of the group with atypical pain the results were equivocal.

8. If a patient has typical angina pectoris clinically, our experience leads us to accept the clinical impression, although the anoxemia test is negative.

9. Hypertension had no apparent effect in statistically increasing the incidence of coronary insufficiency in the group with typical pain, but in the group with atypical pain the reverse was true.

10. The presence of enlargement of the heart in patients with atypical pain increased the likelihood of a cardiac origin of the discomfort.

11. The presence of both hypertension and cardiac enlargement in the group with atypical pain increased the incidence of positive tests, which was the opposite of the results in the group with typical angina.

12. The anoxemia test when electrocardiographically positive can be used as a means of substantiating the diagnosis of coronary insufficiency, and in certain cases, is useful in the differential diagnosis of atypical pain.

13. When patients experience pain during the test but do not have an electrocardiographically positive test, the following factors should be considered in evaluating the weight to be given this manifestation: The similarity of the pain to the spontaneous pain, its prompt occurrence within a short time after beginning of the test, and the nature and reality of the pain as determined by observation of the patient during the occurrence of the pain. Under certain circumstances weight might be given to pain as presumptive evidence of coronary insufficiency. A positive electrocardiographic test, however, is more significant than a negative one, and more significant than the occurrence of pain.

We agree with Levy and his associates that weight should not be given to pain alone in instances when the payment of insurance is involved.

14. The anoxemia test can be used as a method of studying the effect of drugs on the coronary circulation.

15. In certain instances when the anoxemia test is negative, the exercise test may be positive. Great care must be used in subjecting patients to exercise to the point of inducing pain.

16. There were no serious reactions from the judicious use of the test. However, it should not be performed in every patient. Contraindications to the test are congenital heart disease, rheumatic heart disease with valvular damage, pregnancy, myxedema, epilepsy, marked emphysema or other pulmonary disease, severe anemia, and a recent coronary occlusion (within six months). If there is any evidence of congestive failure the test is definitely contraindicated.

17. Our experience with the anoxemia test has paralleled that of others.

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THE ELECTRICAL EFFECTS OF INJURY AT VARIOUS MYOCARDIAL LOCATIONS

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THE introduction of the technique of intracardiac catheterization and the employment of intracardiac catheter electrodes[1,2] have facilitated the study of the electrical influence of the myocardium. It is thus possible to study the electrical changes within the heart cavities produced by subendocardial damage of the outer walls and septum, and by subepicardial damage of the ventricles In the present study this newer technique was used in investigating the genesis of the electrical events established by injury to the heart.

Observations were made on the effect of subendocardial, intramural, and subepicardial injury on the electrocardiogram obtained with exploring electrodes located in the cavities of the heart and on various portions of its endocardial and epicardial surfaces. Attention was focused primarily on the displacement of the S-T segment. However, attention was also given to the T-wave and QRS changes, and observations were made upon the effects of atrial injuries upon the $P\text{-}T_A$ segment.

Two general problems were considered on the basis of the data obtained in this study:

1. *The mechanism of the development of downward displacement of the S-T segment, which is not as fully understood as that of upward displacement.* For example, the cause of downward S-T displacement noted in precordial leads in myocardial infarction, during spontaneous or induced attacks of angina pectoris, in coronary insufficiency, in digitalis medication, and in anxiety states[3] is not fully established.

2. *The significance of the effect of the subendocardial myocardium upon the electrocardiogram.* Some investigators[4,5] have held that this part of the myocardium contributes little. However, there are several recent clinical reports in which localized subendocardial infarction or myocarditis have been related to definite electrocardiographic alterations.[6-9] One case has been reported, for example, with myocardial necrosis of the anterior wall of the left ventricle, most extensive at the endocardial surface, in which downward S-T displacement appeared when a precordial exploring electrode was superjacent to the area of in-

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jury.[6] Although the fundamental postulates of modern electrocardiographic theory, which have recently been summarized,[10] can be used to anticipate the form of the precordial electrocardiogram in cases with localized subendocardial injury, the clinical diagnosis of such involvement is not often made. Discordant views exist as to the effects of subendocardial injury. Previously, and currently, the belief has existed that extensive trauma to the subendocardium produces a downward S-T displacement at all ventricular epicardial surfaces.[3] Another group of investigators believes that such injury leads mainly to a reduction in the QRS complex with inconstant S-T segment changes, and explains this by assuming that the injury effects resulting from subendocardial damage are masked by the normal action currents arising in the uninjured superficial fibers.[11]

Accordingly, the present study was undertaken especially to obtain data upon the role of the subendocardial area of the myocardium in the production of injury currents. With such data it has been possible to re-examine the modern concepts of the genesis of the various deflections generated by injury to the heart and to relate them to the location of the injured region with respect to the exploring electrode.

METHODS

Thirty-one dogs weighing from 8 to 15 kilograms were anesthetized with intravenous pentobarbital sodium (25 mg. per kilogram of body weight). In five animals, the entire anterior chest wall was removed. In the remaining twenty-six, the chest was opened by cutting through the left fifth or sixth intercostal space, and self-retaining retractors provided wide exposure. In all animals subjected to open-chest experiments the pericardial sac was opened anteriorly from apex to base and fastened to the margins of the chest incision. This provided a stabilized cradle for the heart, and permitted ready access to all portions of its surface with the exception only of the extreme posterior basal portion of the left ventricle. These preparations remained viable for eight to twelve hours.

In all experiments unipolar direct leads were used with the indifferent electrodes placed beneath the skin of the left hind paw. The arrangement of the connection of the exploring and indifferent electrodes to the galvanometer was such that in most experiments relative positivity of the exploring electrode caused an upward deflection in the electrocardiogram. Hence, an upward S-T deviation was indicative of a relative positivity of the exploring electrode during this part of the heart cycle. In a few experiments, as indicated in the figures, the reverse connection was used.

Two types of exploring intracavity electrodes were used. The one consisted of a ureteral catheter through which a small (1.0 mm.) enamel-coated copper wire was threaded; a small German silver pellet was soldered to the end of this wire, completely occluding the tip of the catheter. The other was a nonpolarizable exploring electrode. It consisted of a 2.0 mm. glass tube, 20 cm. long, the end of which was tapered and through which extended an ordinary white darning cotton wool wick. Two square knots were tied in the cotton wool

wick which projected about 1.0 mm. from the tapered tip, effectively occluding it. The tube was filled with physiologic saline, and the untapered end was loosely packed with moist cotton. Above this was a Y tube also filled with physiologic saline. The upright limb was sealed with wax through which a nonpolarizable silver-silver chloride electrode, connected to the lead wire of the electrocardiograph, was passed. The other arm of the Y was used to fill the electrode.

The ureteral or the nonpolarizable glass tube electrode was introduced into the right heart via one of the external jugular veins, usually the right. The exact location of the tip of the electrode in the heart was determined by measurement, by direct palpation of the tip, or by gently pushing on the electrode until the tip was seen to cause a bulge in the wall of the ventricle. With the last procedure the electrode, after being located, was withdrawn 1.0 to 1.5 millimeters. The upper end of the electrode was securely fixed in the neck by a stay suture. It was found that the position of the electrode remained constant for hours.

Similar electrodes, specially bent into a rough figure 7, were introduced into the left ventricle through a small slit in the tip of the left atrial appendage. Hemostasis was maintained by a purse-string suture. The extracardiac end of the electrode was securely fixed to the left part of the chest incision by a stay suture. The tip of the electrode was free-lying and located about 1.0 to 1.5 mm. from the endocardial surface.

Control electrocardiographic records were always taken when the electrodes in the right and left ventricle were in place to exclude endocardial pressure injury, indicated by elevation of the S-T segment. This ordinarily could be eliminated, when it occurred, by altering the position of the electrode. In only two experiments was the presence of injury currents in control tracings sufficiently disturbing to require their being discarded.

The epicardial exploring electrodes were also nonpolarizable and consisted of a 2.0 cm. length of cotton wool wick soaked in physiologic saline and fastened to a Y-shaped glass tube filled with physiologic saline. One arm of the Y tube constituted a reservoir to keep the wick constantly well saturated with warm physiologic saline; a silver-silver chloride electrode was placed in the other arm and connected to the lead wire of the electrocardiograph. In some experiments the wicks were fastened to their respective spots by 7-0 atraumatic eye sutures; the experiments were usually delayed from five to twenty minutes until the mild injury produced by the ligature had subsided. In the remainder of the experiments, the injury was obviated by marking a number of spots with a cotton applicator moistened with a drop of India ink and then placing the wicks in contact with the various spots so marked.

When multiple fixed electrodes were used, records were taken from the various electrodes in quick succession by connecting each electrode on the heart surface and in the heart cavities in turn with the indifferent electrode by means of a rotary selector switch.

In some experiments observations were made of the electrical changes at the epicardial surface of the heart by using a moving wick electrode, similar in construction to the stationary wick electrode described. In these experiments,

the exploring wick electrode was moved lightly across that portion of the epicardium to be explored. This gave a continuous record of the changes in potential occurring at contiguous zones on the surface of the epicardium. Control records showed that this moving electrode itself produced no appreciable injury current. When using the moving exploring electrode, marks were made on the electrocardiographic record when the wick passed previously ink-spotted landmarks. In this way the exact location of the shifting electrode could be established from moment to moment on the finished record.

A Cambridge string galvanometer was used in six preparations; in the remainder a Sanborn Cardiette was employed. The sensitivity of the recording system was so modified that each millimeter of deflection represented 2 millivolts in the finished record, that is, 20 millivolts equalled 1 cm. of deflection. This was accomplished with the aid of a simple attenuator.*

Various methods were employed in producing injury. More than one injury was produced in the same heart in some of the animals so as to facilitate study. In such cases adequate time was allowed between experiments for complete recovery indicated by the disappearance of electrocardiographic abnormalities.

Subepicardial injury was produced in several ways (always avoiding grossly visible blood vessels):

1. By superficial suture.
2. By using a pressure electrode as described previously.[14]
3. By local application of (1 to 2 cm.) pads saturated with one-fifth molar potassium chloride solution.
4. By subepicardial injection of 0.5 c.c. of 95 per cent alcohol.
5. By heat cautery, using the red hot head of a metal screw. This gave grossly a sharply demarcated injury 0.8 cm. in diameter and 1.0 to 2.0 mm. in depth.
6. By electrocoagulation.

Subendocardial injury was also produced in several ways:

1. By pressure injury with the exploring electrode introduced into the heart cavities. The end of the electrode was manipulated so as to move it gradually toward the apex of the ventricle and cause it to press against the ventricular wall. A small bulge would be easily visible in the open-chest preparations, allowing control of the extent of injury. After a short period the pressure was gradually released by withdrawing the electrode 1.0 to 1.5 mm., so that the tip lay subjacent to the area of pressure injury. (The same electrical changes were noted when the electrode was in contact with the area of injury as when it was immediately subjacent to it.)
2. By injection of 1.0 to 2.0 c.c. of 95 per cent alcohol or of a one-fifth molar solution of potassium chloride. A long 20-gauge needle was introduced into the myocardium at an acute angle, so that the tip of the needle was at least 3.0 cm. from the point of entry. Minimal or no injury was found overlying or underlying the tip. After a control period of ten to fifteen minutes, the solution

*We are indebted to Arthur Miller, Sc.D., Chief Electrical Engineer of Sanborn Company, for suggesting this attenuator.

was injected subendocardially, the position of the infection being confirmed at autopsy. In several unsuccessful experiments, the solution extended to the epicardium and produced the typical changes of subepcairdial injury. In the successful experiments, the effects of potassium chloride were transitory and the experiment could be repeated after a suitable interval with identical results. The effects of alcohol injection persisted much longer.

3. By scrape. Scrape injury was produced by a 2.0 mm. burr. This was mounted on the end of a curved 2.0 mm. thick metal rod, and introduced into the right ventricle via one of the external jugular veins. In three animals, the burr, on the end of a rod 5.0 cm. long and 1.0 mm. in diameter, was introduced directly through a slit in the tip of the right ventricle. Surprisingly, no injury effects were noted in the intracavity leads from either chamber or from epicardial leads, even when the electrode was within 2.0 mm. of the area of entry following the introduction of the burr. After the control period, lasting up to thirty minutes, the burr was manipulated so that endocardial injury was produced by rotating the burr firmly against the overlying endocardium. By controlling the movement of the free end, and by direct visualization, specifically located scrape injury was produced on the endocarium in particular parts of the right ventricular chamber. This method was adequate and produced consistent electrical changes.

4. By curettage. Curettage of the left ventricle was produced by means of a sharp curet 2.0 by 4.0 mm. which was introduced through a slit in the tip of the left auricular appendage. After control records were taken, injury was produced in specific locations by rotating the curet against the endocardium. Only one such curettage injury was produced in each animal.

In all instances of subendocardial injury, careful necropsy examination was used to confirm the position of injury. Intravenous methylene blue was found useful in identifying the injured region at post-mortem examination. Two centimeters of a 0.5 to 1 per cent solution of an aqueous solution of methylene blue was injected before terminating the experiment. The heart was fixed in formalin solution and examined twenty-four hours later. Injured areas did not take up the dye, and thus were sharply demarcated from the surrounding bluish green uninjured regions.

Records in all cases were taken before injury, immediately after injury, and at varying intervals thereafter.

RESULTS

I. *Effect of Subepicardial Injury on Direct Leads From the Epicardium.*—Subepicardial injury was produced in thirty-six experiments. Tracings were made either with fixed exploring electrodes or with the moving exploring electrode.

The Electrical Changes at the Epicardium Over the Injury: The results were consistent. After injury, a diminution in the depth of the S wave occurred with a simultaneous depression of the T-R (T-Q) segment and an elevation of the S-T segment (Fig. 2,*D*, 3.*A*). In confirmation of previous work from this laboratory,[14] the shift in the level of the T-R (T-Q) segment was usually greater than that of the S-T segment. The ascending part of the R wave persisted,

forming a notch on the upstroke of the full-blown ventricular monophasic deflection, but the total height of the R wave was slightly diminished. Recovery occurred with a reversal of these changes but was accompanied or followed by the development of a deeply inverted symmetrical T wave (first three segments of Fig. 1,*D*). In two experiments the T-wave changes were found to precede the changes in QRS, S-T, and T-R. In one experiment in which a small branch of a coronary artery was tied, preliminary T-wave inversion also occurred (Fig. 1,*D* in box).

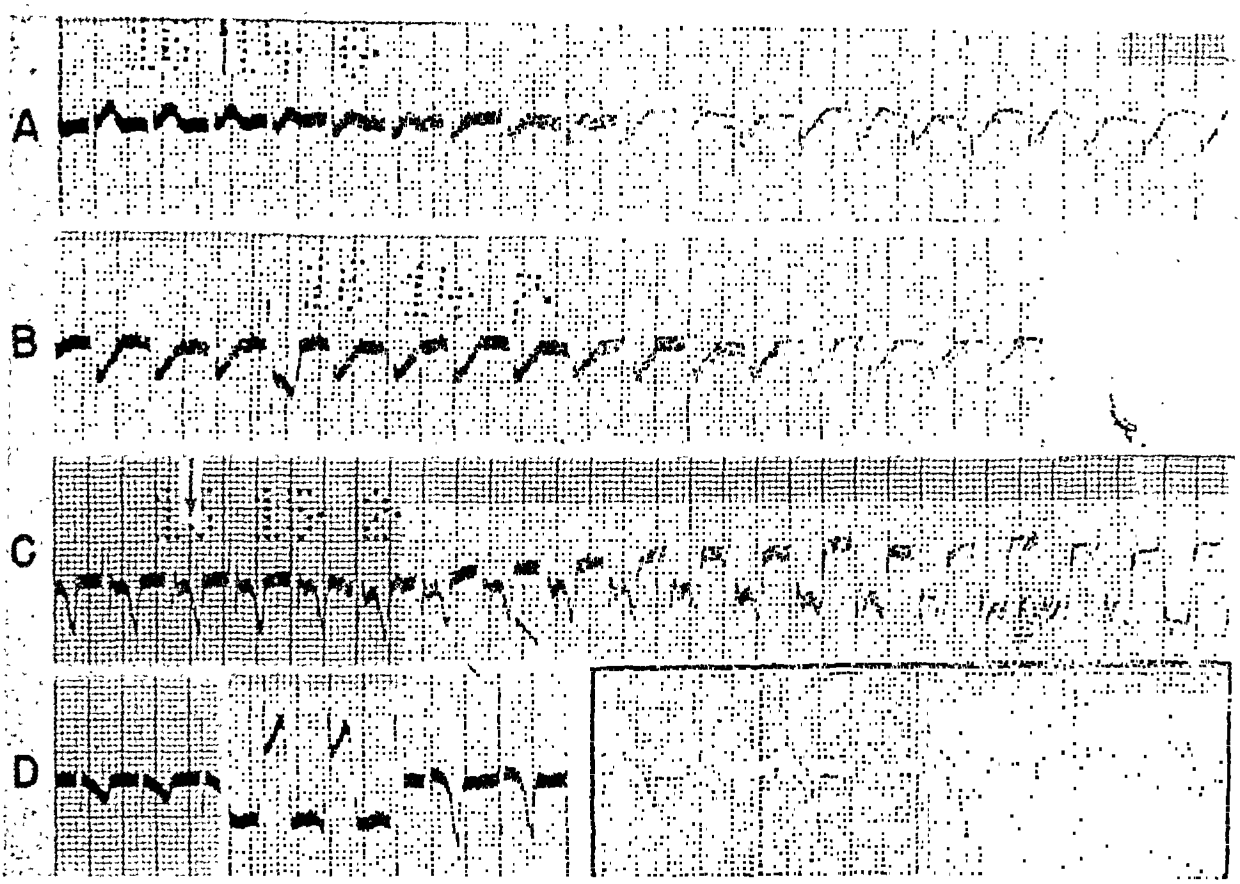

Fig. 1.—Electrical changes occurring within the left ventricular cavity and at its epicardial surface, anteriorly and posteriorly, following subepicardial injury. Rows *A* and *B* show a continuous record obtained with the exploring electrode within the left ventricular cavity. At arrow in *A*, posterior subepicardial injury of the left ventricle was produced. Fifteen minutes after *B*, the contour had returned to that before arrow in *A*. Note the progressive depression of S-T and the decreased amplitude of T which begin at once after injury is produced.

Row *C* shows a continuous record obtained with the exploring electrode on the anterior left ventricular epicardial surface. At the arrow, a posterior subepicardial injury of the left ventricle was produced. Note the progressive S-T depression and the simultaneous T-R elevation following injury.

The first three records in Row *D* were obtained in another experiment with the exploring electrode over the posterior left ventricular epicardial surface. The first record is the control; the second was taken almost immediately after injury of the subjacent subepicardial region; the third was taken fifteen minutes later. Unlike the effect on the exploring electrode within the cavity (*A* and *B*) and on the opposite epicardial surface (*C*), with this location of the exploring electrode there is a marked elevation of S-T (leading to a monophasic ventricular complex). As expected, this is replaced during recovery by a deeply inverted symmetrical T wave.

The last four records in Row *D* (enclosed in box) are from another preparation in which a small branch of the left anterior descending coronary artery was ligated, producing essentially a subepicardial infarct 1.5 cm. in diameter and 0.4 mm. in depth (confirmed at necropsy). The exploring electrode was placed on the epicardium superjacent to the injured area. The four records show, respectively, the control, a record taken immediately after the coronary ligation, and records taken ten and fifteen seconds later. The development of a deep inverted symmetrical T wave precedes the maximum S-T elevation; when the S-T deviation appears, T becomes smaller. Discussed in text.

The Electrical Changes at the Epicardium Adjacent to the Injury and at Distant Epicardial Points: Typical results are shown in Figs. 1 to 3. The results may be summarized as follows:

1. The positive S-T displacement was nowhere as great as over the area of injury.

2. Within the space of a few millimeters from the margin of injury the S-T segment quickly became isoelectric. The zone of isoelectric S-T at the margin of injury was narrow, but was always present.

3. Beyond this zone of isoelectric S-T, the S-T segment was displaced downward. The zone of downward S-T displacement extended over the same surface of the ventricles upon which the injury was located, its extent being dependent upon the size of the subepicardial injury. When the injury was large, the zone of S-T depression occupied the entire surface containing the injury.

4. As the electrode was moved around toward the epicardial surface of the opposite wall of the heart, the downward S-T displacement disappeared and a second zone of isoelectric S-T was found between the opposite walls of the ventricles. This zone of isoelectric S-T was always present regardless of the size of the subepicardial injury.

5. On the epicardial surface of the wall of the heart opposite to that injured, the S-T segment was again displaced downward. The maximum downward displacement of S-T was found in the region located perpendicular to the center of the plane of the injured area.

6. It was found that the regions beyond the periphery of the injured area later showed deeply inverted or large upright symmetrical T waves.

7. With time the T waves increased in amplitude at all points explored regardless of the occurrence of an S-T deviation following injury. At the same time S-T deviations, when they had occurred, lessened and QRS tended to return to its original appearance.

8. Continuous records taken from single points on the epicardium of the wall opposite to that injured showed that the development and regression of the downward S-T displacement was accompanied by the simultaneous development and regression of T-R (T-Q) elevation (Fig. 1,*C*). This is just the opposite of the S-T and T-R deviations found when the exploring electrode is over the subepicardial injury.

9. Lavage of the epicardium with warm isotonic saline solution accelerated the regression of the S-T and T-R displacements. With this saline wash, however, large inverted or upright symmetrical T waves developed in ten to twenty minutes, depending on the location of the exploring electrode.

The Course of Electrical Events at Equidistant Epicardial Points Outside an Area of Subepicardial Injury: In two animals, five ink spots (2.0 cm. apart) were arranged in the form of a cross on the anterior surface of the right ventricle. In four animals, nine equidistant spots (1.5 cm. apart) were arranged to form a square on the anterior surface of the right and left ventricles near the interventricular septum. In two other animals, three equidistant spots (2 cm. apart) were arranged in a straight line along the axis of the pulmonary conus. In one

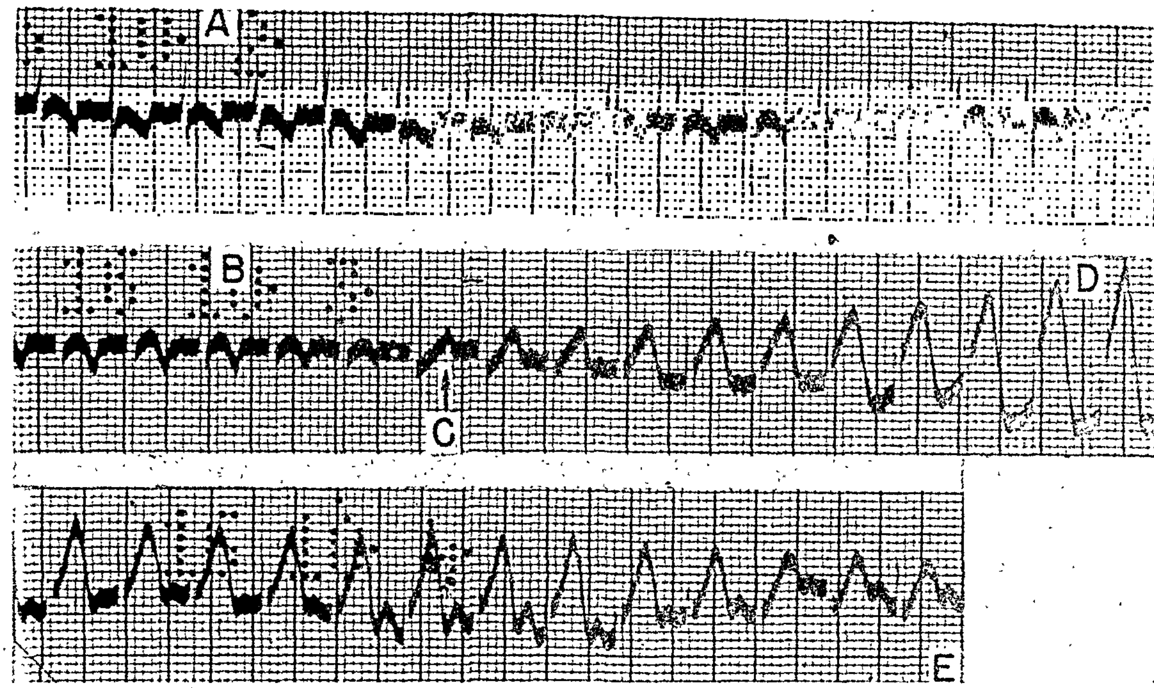

Fig. 2.—Electrical changes occurring at the epicardium in the immediate region of subepicardial injury. Three spots were marked on the epicardial surface of the right ventricular anterior wall. A pad of cotton, 3.0 mm. in diameter, was dampened with one-fifth molar potassium chloride and applied topically to the center point. A continuous record was made while the contact wick electrode was moved from the point near the base to the point near the apex. The three strips are a continuous record (between the middle and bottom strips two beats have been omitted). *A* marks the time when the electrode reached the spot 1.0 cm. basad to the injury; *C*, a spot 2.0 mm. basad; *D*, the region of injury; *E*, 1.0 cm. toward the apex. The S-T segment is isoelectric until *B*, 1.0 to 2.0 mm. from the injury; there S-T becomes depressed for two beats, then again isoelectric for two beats (*C*), and then S-T becomes progressively more elevated at the same time that the T-R segment is progressively depressed. At *D*, a large monophasic ventricular complex is present. In the bottom strip the S-T and T-R segments return quickly to the isoelectric level as the moving electrode passes beyond the injured area. (Unfortunately there is a base line movement here which obscures the shift of S-T.) Discussed in text.

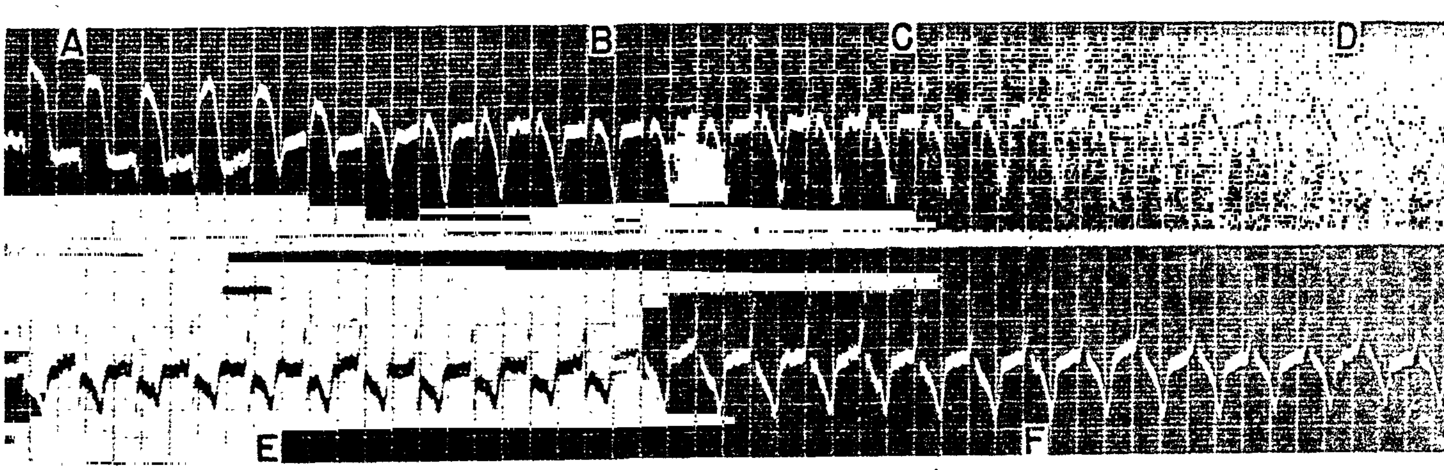

Fig. 3.—Electrical changes occurring at the epicardium following a large epicardial burn injury (2.5 cm. in diameter) located on the posterior aspect of the apex of the left ventricle. A continuous record was made, shown in the two strips, while the exploring wick electrode was moved from the center of the injured area toward the apex and then around its tip to the anterior wall and beyond the interventricular groove toward the base of the right ventricle. *A* marks the time the electrode was over the center of the injury; *B*, just beyond the periphery of the burn (which appeared normal grossly); *C*, over the tip of the apex; *D*, over the anterior apical surface of the left ventricle; *E*, over the interventricular groove; *F*, over the anterior surface of the right ventricle. Post-mortem examination revealed the burn injury to be mainly subepicardial with hemorrhagic strands extending to the subendocardium. Over the injured area (*A*) there is a small Q wave, marked S-T elevation, and less T-R depression, giving rise to a monophasic curve. As the electrode reached the edge of injury (*B*), the S-T and T-R deviations disappeared and a progressively increasing inverted T wave appeared. The S-T segment at the tip of the apex (*C*) is isoelectric, but over the anteroapical part of the left ventricle (*D*) it becomes depressed; this depression increases over the interventricular groove (*E*) and then lessens and disappears over the anterior wall of the right ventricle (*F*). An intracavity exploring electrode in the tip of the left ventricle near the burned area showed S-T elevation which is attributed to the incomplete transmural injury found at necropsy. Discussed in text.

animal, three such equidistant spots were marked on the anteroapical wall of the left ventricle.

After control records were taken, localized subepicardial injury was produced in each preparation at the center spot. In two animals, alcohol was used. The injury usually measured 0.5 to 0.8 cm. in diameter and was from 1.0 to 2.0 mm. in depth. The remaining spots, therefore, were well outside the margins of the injured area. In four animals a superficial suture was used which produced an injured area of 1.0 to 2.0 millimeters. In the remaining three animals a cautery was used to create an injured area 0.8 cm. in diameter and 1.0 to 2.0 mm. in depth. Records were taken immediately after the production of injury and repeated at lengthening intervals until the records showed a return to the normal contour, a period varying from one to two hours. The findings in all but one experiment were similar and a typical one is shown in Fig. 4.

The results of this group of experiments on subepicardial injury confirm and amplify the findings previously reported from this laboratory,[14] and can be summarized as follows:

1. Changes in the contour of the QRS complex described in the preceding section, indicating an alteration in the pattern of impulse spread, occurred first in the injured area and later also in other areas outside the injured region.

2. An elevation of the S-T segment occurred which was maximum over the injured region and became smaller in regions removed from the injury. These S-T changes tended to disappear with time. The S-T displacement occurred sooner and to a greater extent at points nearer the base than at points nearer the apex of the heart. One experiment which was an exception, the three equidistant points being on the anteroapical wall of the left ventricle and the injury being produced by suture, showed a greater injury effect in the apically than in the basally located point. This exception may be explained by an inadvertent ligation of a small blood vessel supplying the apical portion of the heart. As would be expected, in the experiments with eight distant exploring electrodes, the magnitude of the injury effects varied with the distance from the site of injury.

3. A deeply inverted symmetrical T wave appeared some time after injury was produced, both in the region of injury and in the surrounding regions. These deeply inverted T waves developed in the areas surrounding the injury regardless of whether or not S-T displacement had occurred. These T waves tended to disappear with time.

These injury changes which appear after a lag in the zone surrounding injury may be related to the spread, by diffusion or by lymphatics, of the products of injury. It must be emphasized that all the points were located on the wall injured.

Only in two experiments did the points not all lie in the same plane. In these experiments cautery injury was produced in the middle of five equidistant points arranged in a straight line along the pulmonary conus. Four of the points lay on the anterior surface of the heart; the fifth, near the lateral margin of the right ventricle, lay on its lateral wall. Elevation of the S-T segment occurred at the point of injury and at the points on the anterior wall. However, the

point on the right lateral border showed S-T depression, as had been found in experiments described in the preceding section in which the electrode was placed on the wall of the heart opposite to that injured.

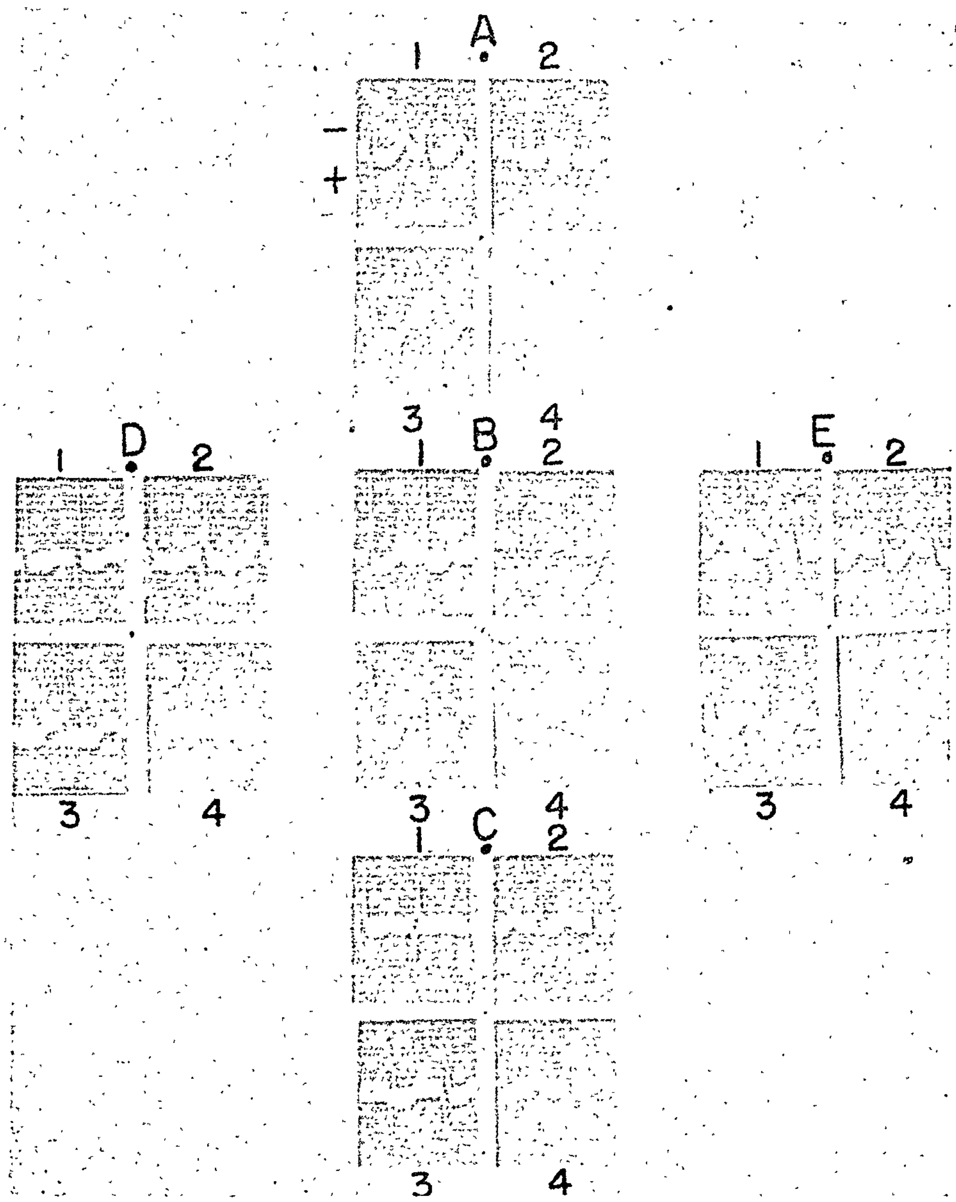

Fig. 4.—Spread of subepicardial injury effects. Note that the polarity used in this experiment was the reverse of that shown in Figs. 1 to 3 so that an S-T depression here is equivalent to an S-T elevation in the preceding figures. Relative negativity of the exploring electrode in this experiment gave an upward deflection instead of a downward one as in the previous figures.

The five groups of records show the control (*1*), and records taken, respectively, immediately, five minutes, and forty-five minutes after injury (*2*, *3*, and *4*). Subepicardial injury, 8.0 mm. in diameter, was produced at Site *B* in the center of the anterior surface of the right ventricle by heat cautery. The other four sites were each 2.0 cm. distant from this center spot and 90° from each other. They were all equidistant from the edge of injury. No gross blood vessels were visible at the site of injury. Site *A* was near the A-V sulcus; *C*, near the apex of the right ventricle; *D*, near the lateral border of the right heart; *E*, near the pulmonary conus. It will be noted that, as expected, the S-T displacement is greatest over the injury (*B*) and is unequal in the four other equidistant spots (*A*, *C*, *D*, and *E*). Thus, for example, the S-T depression is least in *C* and greatest in *A*. Furthermore, the evolution of the S-T deviation in time was not uniform. In the four distant sites the S-T deviation is maximum at five minutes (Segments *3* in *A*, *C*, *D*, and *E*) while over the injury it is maximum immediately after injury was induced (Segment *2* in *B*). Furthermore, at Site *E*, the S-T deviation persisted for forty-five minutes while at the other distant sites (*A*, *C*, and *D*) it had practically or entirely disappeared by this time. The spread of injury is thus unequal and its evolution in equidistant spots nonuniform. Discussed in ext.

II. Effect of Subepicardial Injury on Intraventricular Leads.—Twenty-two different experiments were performed in ten animals, injury being produced by cautery or topical one-fifth molar potassium chloride. In five animals, records were obtained from both right and left cavities; in the remaining five, records were obtained only from the right ventricular cavity. Before a second experiment was performed in the same animal, sufficient time was allowed for complete recovery from the injury effects of the previous experiment.

In all but one of these experiments the changes in the tracings were of the same type. A typical result is shown in Fig. 1,*A* and *B*. The changes consisted of an immediate depression of the S-T segment, with the T-R (T-Q) segment remaining practically isoelectric, the T wave upright, and the QS becoming slightly smaller. With recovery, the S-T segment returned to its isoelectric level and the QS returned to its previous size or became slightly larger than in the control electrocardiogram. At the same time the T wave became more inverted and developed a symmetrical configuration. These T waves sometimes appeared before the S-T had returned to its isoelectric level.

In one experiment, in which an area of injury was produced on the anterior surface of the right ventricle by cautery, a tall upright T wave appeared in records from the right ventricular cavity, without any S-T elevation and only 0.5 mm. decrease in the depth of QS. This was the immediate effect. Three minutes later the S-T segment became elevated, and the T wave became even taller. Complete recovery occurred in fifty-five minutes. Autopsy examination revealed a subepicardial area of coagulation 2.0 cm. in diameter and 2.0 mm. deep. However, in the subjacent subendocardial myocardium, there were multiple minute areas of hemorrhage. It is not unreasonable to assume, therefore, that this unusual change in the intracavity lead was due to the subendocardial damage secondary to the transmitted heat. This is illustrated diagrammatically in Fig. 17 (lower left hand drawing).

In two experiments, subepicardial burn injury was produced on the lateral wall of the left atrium and its appendage. A tracing taken from the middle of the left atrial cavity showed depression of the P-Q ($P-T_A$) segment. The changes in the atrial cavity following subepicardial atrial damage, therefore, are analogous to the S-T depression in the ventricles following ventricular subepicardial injury. The $P-T_A$ segment is the atrial analogue of the S-T segment of the ventricles. Thus, injury of the atria operates similarly to injury of the ventricles.

III. Effect of Subendocardial Injury of the Outer Walls of the Ventricles on Endocardial and Intracavity Leads.—Subendocardial injury was produced by pressure electrodes introduced into the heart cavities forty-five times in eleven animals with the same results. A typical experiment is shown in Fig. 5. The following reversible changes were noted:

1. A decrease in the amplitude of the QS, so that it formed a notch on the upstroke of the full-blown monophasic ventricular deflection (Fig. 16, Chart 5).
2. A depression of the T-R (T-Q) segment.
3. An elevation of the S-T segment.

4. The extent of the S-T and T-R displacements was not equal. However, the pattern of development and disappearance of T-R was similar to that of S-T (Fig. 16, Charts 3 to 6). In some experiments the T-R depression was great while the S-T elevation was less than 1.0 millimeter. Occasionally, the opposite occurred. Sometimes the amount of displacement of S-T and T-R was equal. However, in the majority of experiments, the shift of the T-R was greater than that of the S-T segment.

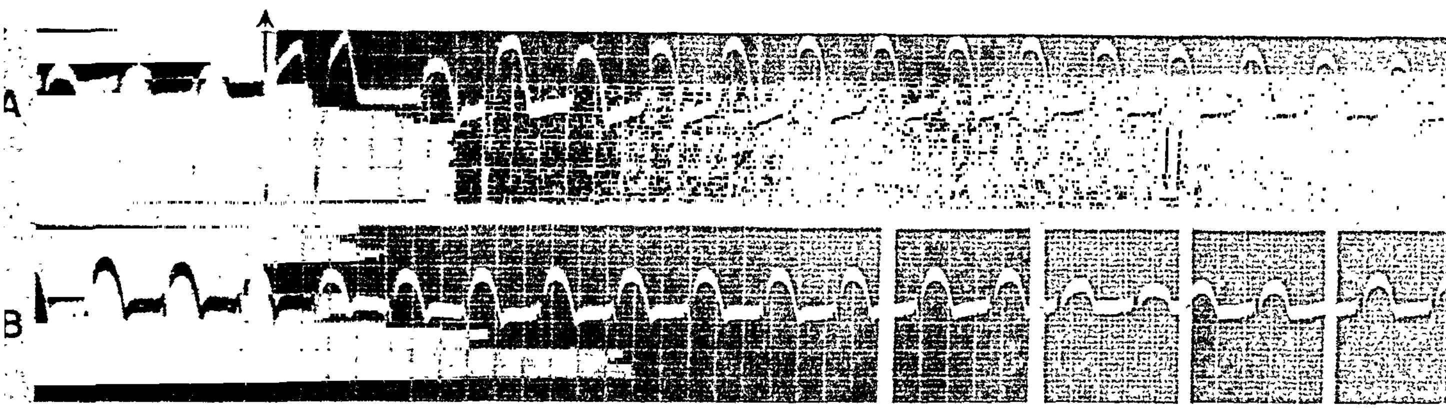

Fig. 5.—Electrical changes occurring at the endocardium of a subendocardial injured area. Subendocardial injury of the right ventricle was produced by endocardial pressure with an exploring electrode. Strip *A* and the first part of Strip *B* are a continuous record. The period of electrode pressure is shown by the two arrows in Strip *A*. The last four segments of Strip *B* were taken twelve seconds, twenty-four seconds, one minute, and fifteen minutes after release of pressure, respectively. With pressure, two successive ventricular premature systoles appear and are followed, after a normal beat, by a third premature systole. Note the development of S-T elevation and the lesser degree of T-R depression following injury and beginning regression even while pressure was maintained. Injury also led to the transient disappearance of the S wave. Restoration of the original contour is progressive and is almost complete within one minute after release of the pressure. These results parallel those previously observed with a similar electrode applied epicardially.[14] Discussed in text.

5. The persistence of the residual injury effects increased with more severe injury. Thus, after pressure for five seconds, complete restoration occurred in one beat; after pressure for four minutes complete restitution required twenty-two minutes. Occasionally, slight S-T elevation remained as a residue. Necropsy revealed areas of subendocardial hemorrhage measuring about 0.3 to 0.8 cm. in diameter, when endocardial pressure injury was produced repeatedly in the same site.

6. At the onset of the subendocardial pressure injury, several premature beats with widened QRS complexes occurred, followed by typical T-R, S-T, and QS changes (Fig. 5,*A*). These premature beats probably originated locally at the margin of injury.[15] In several instances, normally spaced beats with widened QRS complexes occurred with injury and disappeared when the pressure was released. These probably represent local focal intraventricular block (Fig. 6,*A*, *B*, and *C*).

7. In only two experiments, with mild pressure, did deeply inverted T waves occur without deviation of the S-T segment. However, when the pressure was increased the usual T-R and S-T changes developed. In another experiment, the S-T changes were slight while the T wave became significantly deeper after prolonged pressure injury. In still another experiment, the T wave became

deeper before the monophasic ventricular injury curve appeared. In a fifth experiment, the T wave became deeper during recovery from the injury effects.

Similar changes were obtained with other methods of subendocardial injury (Fig. 7, Row 3, and Fig. 17, lelt middle chart).

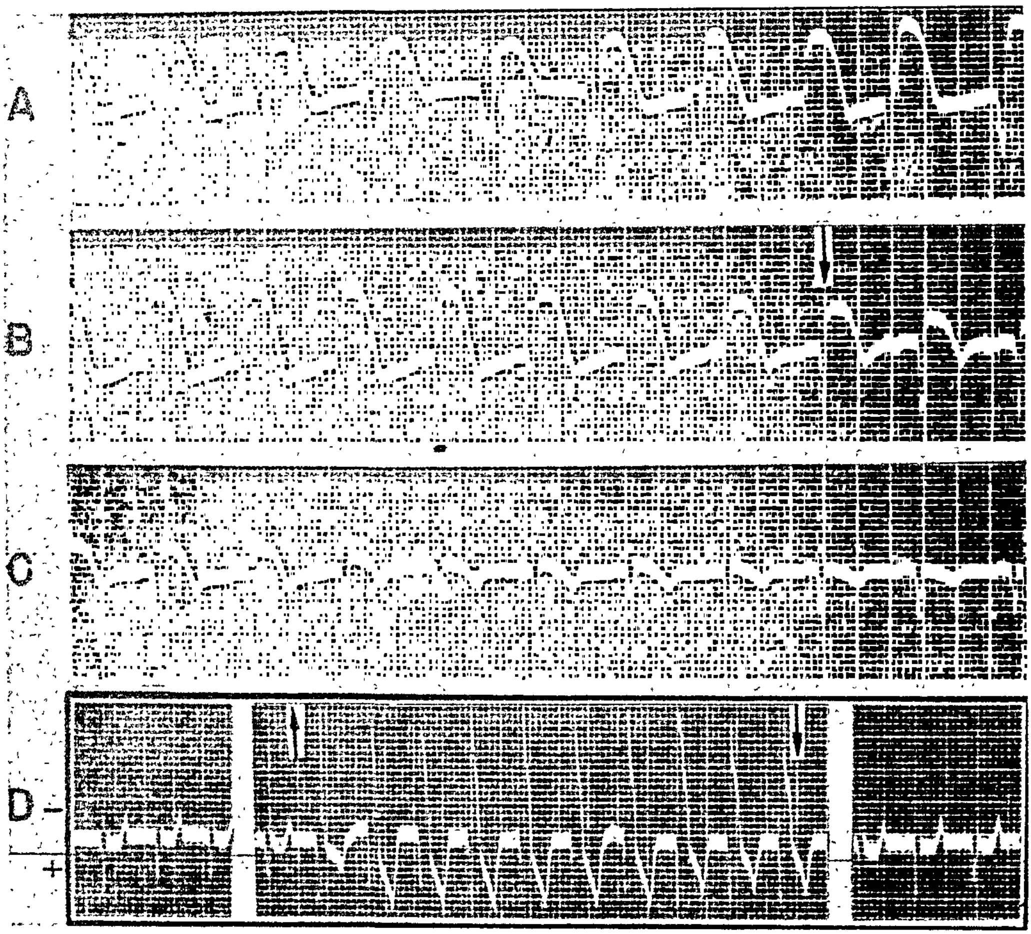

Fig. 6.—Production of local focal intraventricular block by endocardial pressure injury in the right ventricle. Rows *A*, *B*, and *C* represent a continuous strip of the first experiment. In this dog with closed chest, subendocardial injury was produced by the same kind of pressure electrode as that used in Fig. 5. Injury was produced before Record *A* was taken and the pressure gradually lessened. Arrow in *B* shows end of pressure. The last beats in *C* can serve as a control since this was the contour found before pressure was applied. Note that, unlike endocardial leads in animals with open chests, in which T is upright, the T wave is inverted in this animal with closed chest. With maximal pressure, in *A*, the QS widens, returning to its normal duration upon release of pressure. In Strip *B*, QS, after pressure release, becomes smaller, returning to its control depth as recovery continued (*B* and *C*). Injury in this case, as in Fig. 5, caused S-T elevation and a lesser degree of T-R depression which progressively lessened during recovery. A sinus arrhythmia is present. The preliminary QRS widening is attributed to a prolongation of depolarization in the injured area; a local focal intraventricular block.

In the second animal, with chest open, (Row *D*) endocardial injury was applied by pressure and the exploring electrode was placed on the superjacent epicardium. The first segment is the control. The middle segment shows, between arrows, the production of subendocardial injury. The last segment shows the recovery; two beats are omitted between the middle and last segments. In this instance, the entire alteration of pressure injury is dominated by the local focal intraventricular block; QRS is broadened and the ST-T is deviated in a direction opposite to QRS. It is apparent that local focal intraventricular block produced in the subendocardium may be recorded from the superjacent epicardial area. In this experiment, as in Fig. 4, the polarity of the electrodes was reversed. Discussed in text.

In two experiments, subendocardial injury was produced in the right atrium with a pressure electrode. This caused a positive deviation of the P-Q (P-T_A) segment, with its return to control levels upon relief of pressure (Fig. 15). This again is analogous to the S-T changes obtained with similar pressure on the endocardium of the ventricles.

IV. Effect of Subendocardial Injury on Direct Epicardial Leads.—Subendocardial injury was produced by pressure electrodes introduced into the heart cavities in eleven animals, by the subendocardial injection of 95 per cent alcohol in four animals and of one-fifth molar potassium chloride in four animals, by curet in three animals, and by scrape in six animals. These injuries were confined to the outer walls of the ventricles, exclusive of the interventricular septum.

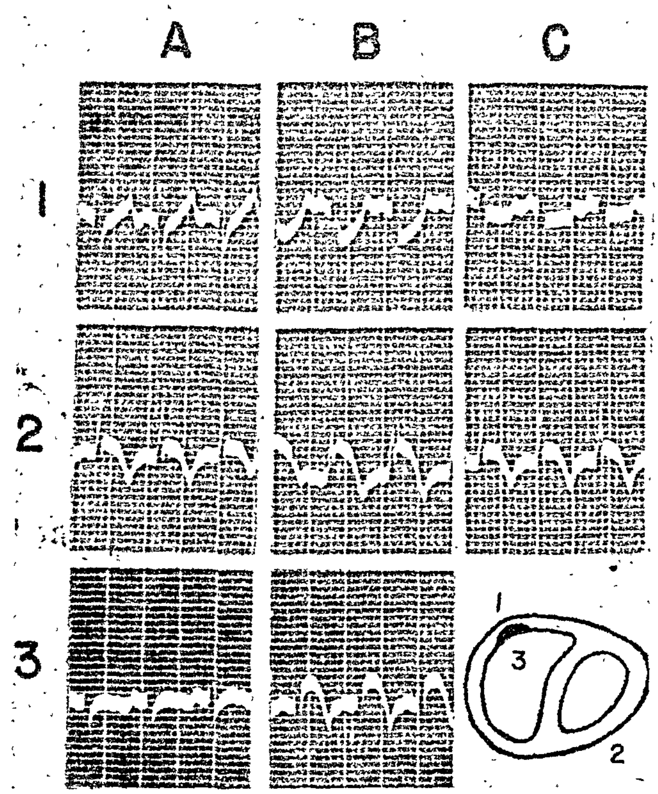

Fig. 7.—Electrical changes occurring at the epicardium superjacent to a subendocardial injury, at the posterior epicardium of the left ventricular apex, and in the right ventricular cavity following injury (by scrape) of the subendocardium of the anterior right ventricular wall. The diagram in the lower right-hand corner shows the location of injury and the position of the three exploring electrodes. The numbers correspond to the rows showing the records obtained with the exploring electrode in the three locations. Column *A* shows the control; *B* and *C* are records taken, respectively, immediately and nine minutes after the injury was induced. Following injury (Column *B*), an S-T depression develops when the electrode is on the epicardium over the subendocardial injury (Row *1*), and an S-T elevation appears when the electrode is in the right ventricular cavity (Row *3*) and posterior epicardial surface of the left ventricle (Row *2*). At the same time R becomes smaller in Position 1, and S disappears in Position 2. Discussed in text.

Electrical Changes Produced at the Epicardial Area Over the Subendocardial Injury: Consistently, a depression of the S-T segment and minimal diminution in the amplitude of the R and S wave followed injury (Figs. 7, Row 1, 10, Row 1, 11, Row 2, and 12,*B*). In one experiment, a tall upright symmetrical T wave appeared. (Only when the injury extended to involve the subepicardium were

these typical changes absent and the findings of subepicardial injury noted instead.)

Occasional premature beats with wide QRS complexes were seen in tracings made while the injury was being produced. In two animals, subendocardial pressure injury produced by the pressure electrode resulted in the appearance of widened QRS complexes occurring at the same rate as in the control records (Fig. 6,*D*). These beats are similar in character to those described in the preceding section and probably, like them, signify local focal intraventricular block.

Electrical Changes Produced at Epicardial Areas Distant From the Subendocardial Injury: In these experiments data were obtained by recording either with fixed or moving exploring electrodes. Typical results are shown in Figs. 7, Row 2, 10, Rows 2 and 3, 11, Row 1, and 12.

As the electrode was moved away from the epicardial region overlying the subendocardial injury, the S-T depression became less marked and eventually disappeared. As the electrode was moved to the epicardial surface of the opposite wall, S-T became elevated and its elevation increased until a zone was reached 180 degrees from the point of subendocardial injury. Thus, subendocardial injury of the anterior wall of the right ventricle caused an upward S-T deviation in epicardial leads from the posterior wall of both the right and left ventricles. Subendocardial injury of the posterior wall of the left ventricle caused S-T elevation in leads from anywhere on the anterior wall of the ventricles and the S-T segment was isoelectric in leads from the lateral wall of the ventricles. The magnitude of the zones of downward and upward S-T displacement was roughly proportional to the area of injury. In the majority of experiments the magnitude of the depression of S-T over the region of injury was greater than its elevation at distant points. However, in several experiments the S-T displacement at a distance was equal and opposite to the S-T displacement over the injury In one remarkable experiment where a very extensive subendocardial injury was produced in the anterolateral wall of the right ventricle, marked S-T elevation took place at the lateral margin of the left ventricle with only slight, though definite S-T depression over the area of injury (Fig. 11).

V. Effect of Subendocardial Injury of One Side of the Interventricular Septum on Epicardial and Intracavity Leads.—Localized scrape injury was produced on the right side of the interventricular septum in three animals and on the left in two. The injured areas measured from 1.5 to 2.5 cm. in diameter, and consisted of roughened endocardium with hemorrhage into the subendocardial myocardium extending for a depth of from 1.0 to 3.0 millimeters. Ventricular fibrillation was easily produced by injurying the basal part of the interventricular septum, expecially on the right side. Single or serial electrical shock[16,17] was successful in breaking such ventricular fibrillation without producing detectable epicardial damage. In one animal, ventricular fibrillation occurred when the probe was introduced into the heart via the jugular vein. A single electric shock broke the fibrillation. Subsequent control records revealed no injury effects on the epicardial surfaces or within the cavities.

Typical results are shown in Figs. 8 and 9 and diagrammatically in Fig. 17 (last two drawings of middle row). In all experiments the expected effects occurred in ipsilateral intracavity leads. These were the same as when

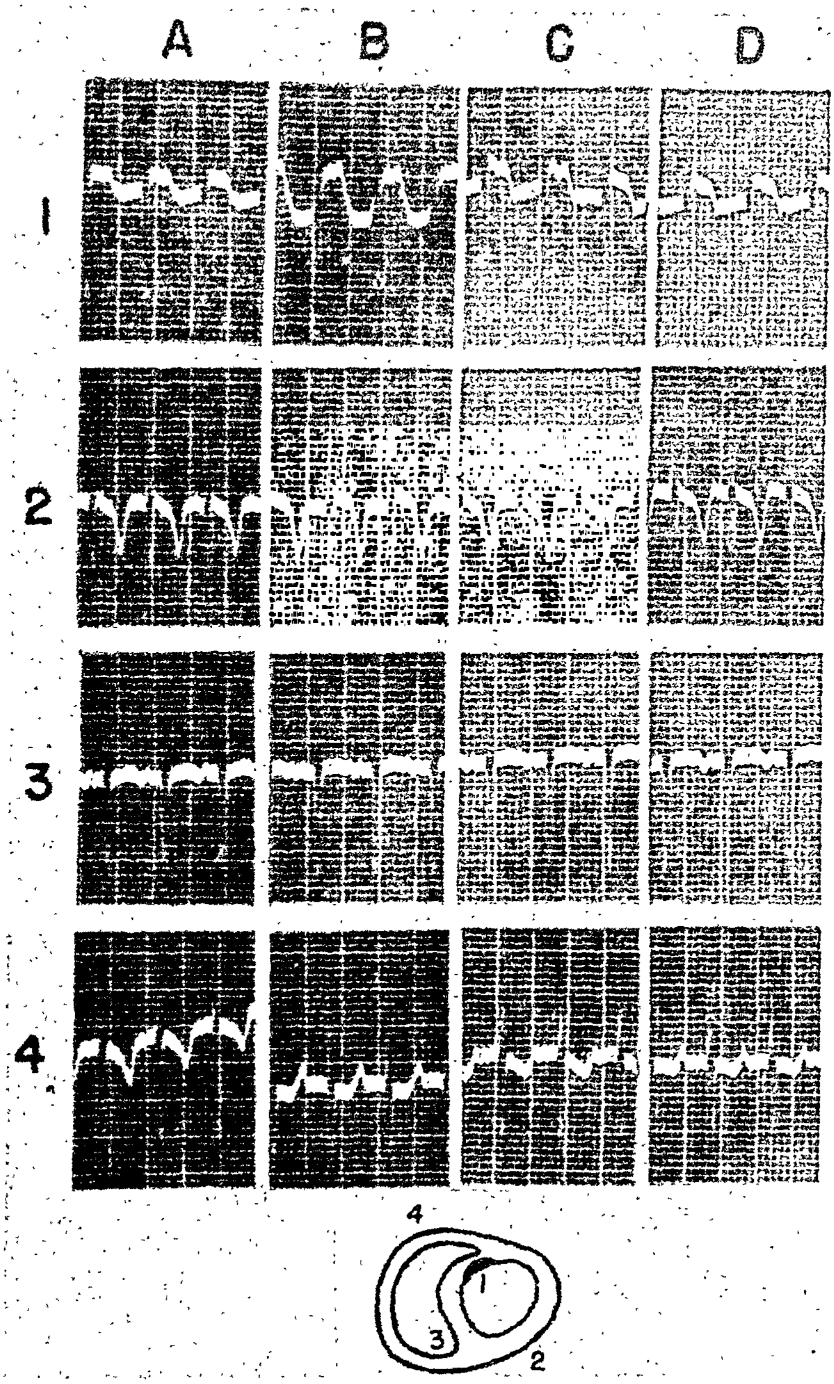

Fig. 8.—Effect of injury (by scrape) of subendocardium of anterior basad part of left side of interventricular septum. Arrangement of figure as in Fig. 7. Diagram shows location of injury and position of four exploring electrodes employed: *1* is in left ventricular cavity; *2*, on the epicardial surface of anterolateral wall of the left ventricle; *3*, in right ventricular cavity near its apex; *4*, or the epicardial surface of anterior wall of right ventricle. Rows *1* to *4* show, respectively, the records obtained with the exploring electrodes in these four sites. Column *A* represents the control; *B*, *C*, and *D* were taken, respectively, immediately, five, and ten minutes after the septal injury was produced. Following injury there is a definite S-T elevation in a lead from the left ventricular cavity (Row *1*) and a slight elevation of S-T when the electrode was over the epicardium of the left ventricle (Row *2*); at the same time there is S-T depression with the electrode over the epicardium of the right ventricle (Row *4*). No S-T deviation occurred in a lead from the apical part of the right ventricular cavity (Row *3*). These results, like those of the preceding experiments, are expected on the basis of the spatial relationships of the electrodes to the injury. Discussed in text.

subendocardial injury was produced in the outer walls of this ventricle. An upward S-T displacement occurred. At the same time there was a downward S-T displacement in the contralateral intracavity lead. In one experiment, however, no change was noted in the contralateral intracavity lead. In this animal

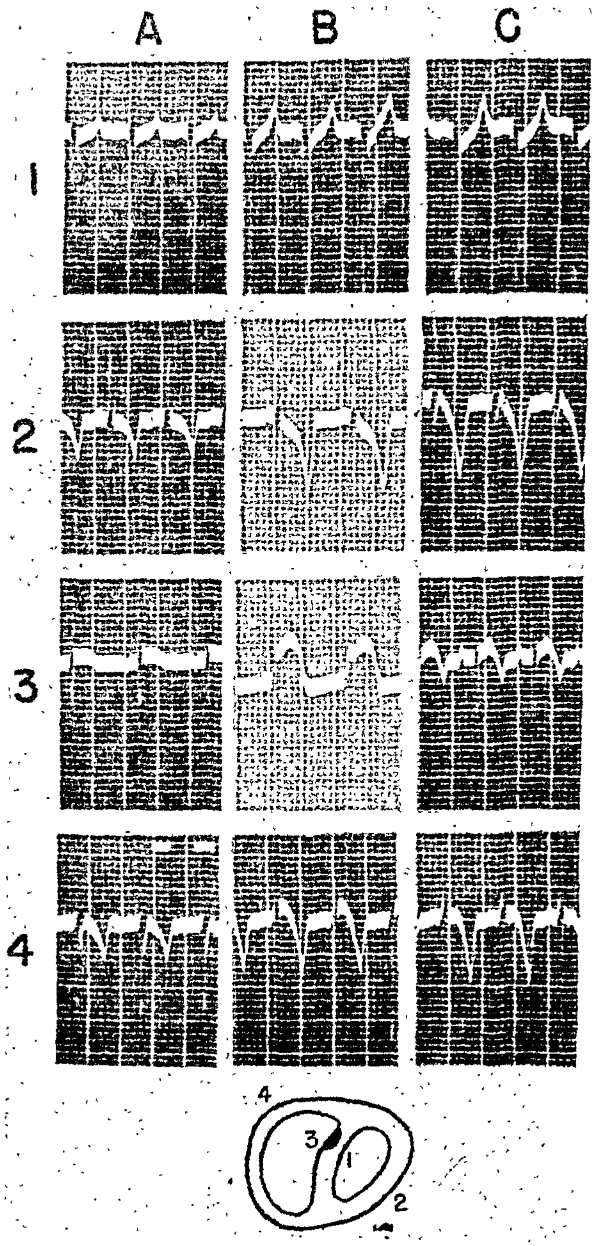

Fig. 9.—Effect of injury (by scrape) of the subendocardium of the right side of interventricular septum. Arrangement of figure as in Fig. 7. Diagram shows location of injury and position of four exploring electrodes employed: *1* is in left ventricular cavity; *2*, on the epicardial surface of antero-lateral wall of left ventricle; *3*, in right ventricular cavity; *4*, on the epicardial surface of *anterior* wall of right ventricle. Rows *1* to *4* show, *respectively*, the records obtained with the exploring electrodes in these four sites. Column *A* represents the control; *B* and *C* were taken, respectively, immediately and ten minutes after the septal injury was produced. Following injury there is a definite S-T elevation in a lead from the right ventricular cavity (Row *3*) and to a lesser extent in a lead from the epicardium of the right ventricle (Row *4*); at the same time there is S-T depression in a lead from the left ventricular cavity (Row *1*) and over the epicardium of the left ventricle (Row *2*). Discussed in text.

the injury was produced in the upper part of the left side of the interventricular septum (Fig. 8). At autopsy it was found that the septum bulged into the right ventricle, and that the intracavity electrode was located in the tip of the right ventricle, so oriented that it was distant from the injury and lying in the plane parallel to the major edge of the injury. Thus, with the exception noted, injury of the subendocardium of the interventricular septum caused opposite changes in the S-T segment in the two ventricular cavities.

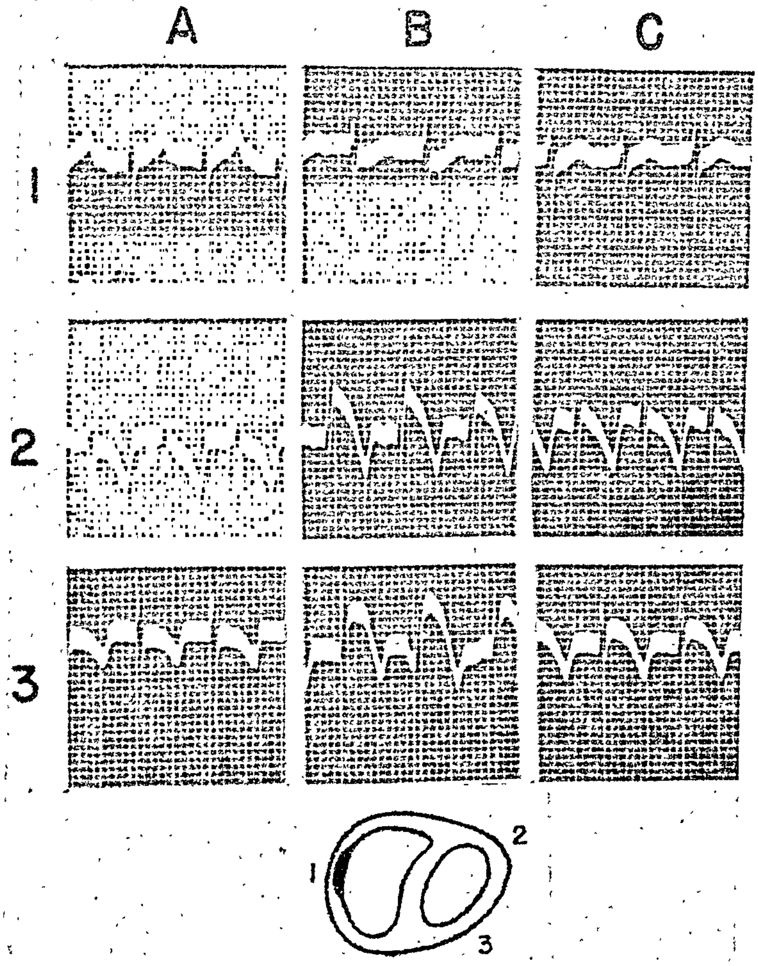

Fig. 10.—Effect of injury (by scrape) of the subendocardium of the anterolateral wall of the right ventricle. Arrangement of figure as in Fig. 7. Diagram shows location of injury and position of three exploring electrodes employed: *1* is on the epicardial surface superjacent to the endocardial injury; *2*, on the epicardial surface of the anterolateral apical wall of the left ventricle; *3*, on the epicardial surface of the posteroapical wall of the left ventricle. Rows *1* to *3* show, respectively, the records obtained with the exploring electrodes in these three sites. Column *A* represents the control; *B* and *C* were taken, respectively, immediately and three minutes after the endocardial injury was produced. Following injury there is a definite S-T depression in a lead from the epicardial surface superjacent to the endocardial injury (Row *1*) and definite S-T elevation in leads from the other two epicardial spots (Rows *2* and *3*). This experiment also shows the typical quick restitution found with subendocardial injury which contrasts with the longer persistence of injury effects after epicardial injury. The injury effects are almost entirely gone in three minutes (Column *C*). Discussed in text.

In the epicardial leads, the changes in S-T following subendocardial injury of one side of the interventricular septum were as follows: Injury of the right side of the interventricular septum produced slight elevation of the S-T segment of the right anterior ventricular wall as well as in the right ventricular cavity,

and slight depression of the S-T segment of the anteroapical epicardium of the left ventricle as well as in the left ventricular cavity. Conversely, injury of the left side of the interventricular septum caused an elevation of the S-T segment in leads from the epicardium of the left ventricle as well as from the left ventricular cavity, and a depression of the S-T segment at the anterior epicardium of the right ventricle as well as in the right ventricular cavity.

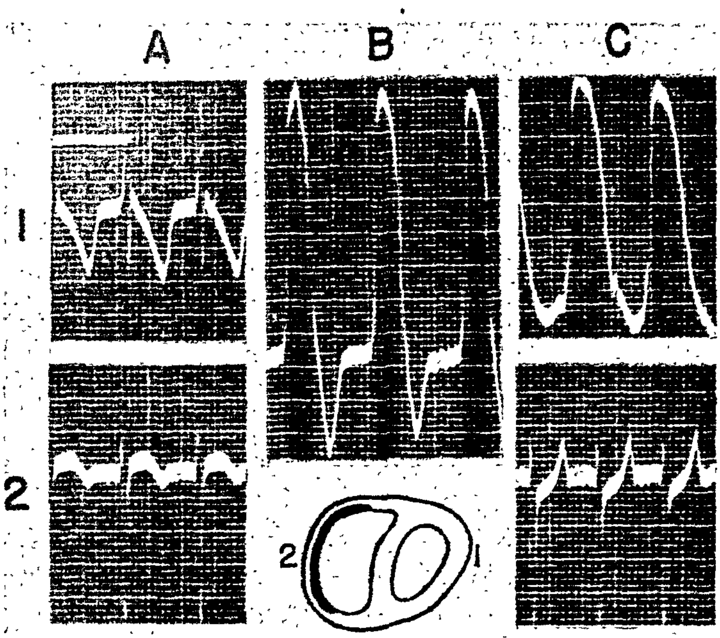

Fig. 11.—Effect of extensive subendocardial injury (by scrape) of the entire anterolateral wall of the right ventricle. The area at necropsy measured 3.0 by 5.0 centimeters. Arrangement of figure as in Fig. 7. Diagram shows location and extent of injury and position of two exploring electrodes employed: *1* is on the epicardial surface superjacent to the middle of the subendocardial injury; *2*, on the epicardial surface of the lateral wall of left ventricular apex. Rows *1* and *2* show, respectively, the records obtained with the exploring electrodes in these two sites. Column *A* represents the control; *B* and *C* were taken, respectively, immediately and two minutes after the endocardial injury was produced. (No record was obtained for Site *2* immediately after injury.) Following injury extremely marked S-T elevation developed in the lead made at the epicardial surface of the left ventricle (Row *1*) and much less marked S-T depression appeared in the lead made at the epicardium superjacent to the endocardial injury (Row 2). Thus, the injury effects were more marked in this case on the opposite uninjured ventricle, at which site a huge monophasic ventricular complex appeared. Ventricular fibrillation occurred three minutes after the records of Column *C* were obtained. Discussed in text.

VI. Effect of Transmural Injury on Epicardial and Intracavity Leads.—

Incomplete Transmural Injury: The entire thickness of the ventricular wall was injured in four animals, but in these, normal muscle was found to be present, interspersed with the injured muscle. The results in the four experiments were similar.

In one of these animals, subendocardial injury was first produced by alcohol injection, and later injection of an additional amount led to S-T elevation in the overlying epicardium as well as within the cavity itself (Fig. 17, lower right hand diagram). Post-mortem examination revealed the entire thickness of the wall in the region of the injection to be mottled yellowish gray with minute reddish brown areas of normal-appearing myocardium. This indicated that some normal subendocardial muscle was present.

In three animals an area of cautery injury was produced. For example, in one of these the injury was on the anterior wall of the right ventricle. The record from the right intracavity lead showed a decreased size of the QS, an upward displacement of the S-T segment, and a deeply inverted T wave. Recovery was complete in fifty-five minutes. Post-mortem examination revealed an area of injury 2.0 cm. in diameter, with necrosis of the subepicardial muscle to a depth of 1.0 mm. and hemorrhage in the subjacent subendocardial muscle, portions of which appeared normal.

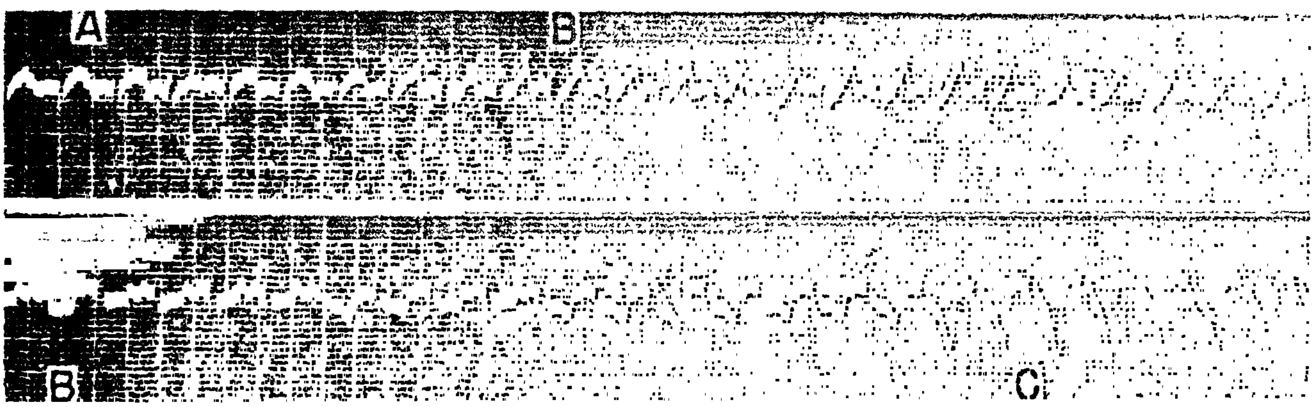

Fig. 12.—Electrical changes occurring at the epicardium superjacent to a subendocardial injury (by scrape) of the anterior wall of the right ventricle (injured area, 1.0 cm. in diameter). The two strips show a continuous record obtained by shifting the exploring wick electrode from a point (*A*) 1.0 cm. away from the edge of injury toward the injured area (between points labelled *B*) and to a point 1.0 cm. beyond the injury (*C*). The S-T segment is isoelectric at *A*, becomes depressed over *B*, and this depression lessens at *C*, tending to approach the isoelectric level at the end of the strip. The T-wave contours in this figure are similar to those seen in the several regions before injury was produced and are, therefore, not attributable to the subendocardial injury. Discussed in text.

Complete Transmural Injury: In two animals heat coagulation of a large area (2.5 by 5.0 cm.) of the anterior wall of the right ventricle (Fig. 14) was produced by holding a red hot soldering iron firmly against it for two minutes. Surprisingly, the heart continued to beat regularly. A continuous record was obtained from a subjacent electrode within the right ventricular cavity while the injury was produced (Fig. 13, *A*, *B*, and *C*). The changes were slight. The T wave became slightly smaller. No QS or S-T alterations were noted. An unusual notching appeared on the T wave in the intracavity lead which disappeared in four to five minutes (Fig. 13,*C*). An epicardial lead from the center of injury revealed complexes identical with those from the right cavity lead (Fig. 13,*D*, last strip), although electrical alternans (of the S-T segment and T wave) appeared. In the second animal an electrical alternans involving only the S-T segment and T wave was observed (Fig. 13,*E*). This preceded spontaneous ventricular fibrillation. Epicardial leads from uninvolved portions of the right ventricle in this animal and from the anterior left ventricle showed no significant S-T deviation.

The results in these two animals indicate that total destruction of the entire area of injury produces a "hole" through which the epicardial electrode "drains" the intracavity potentials.

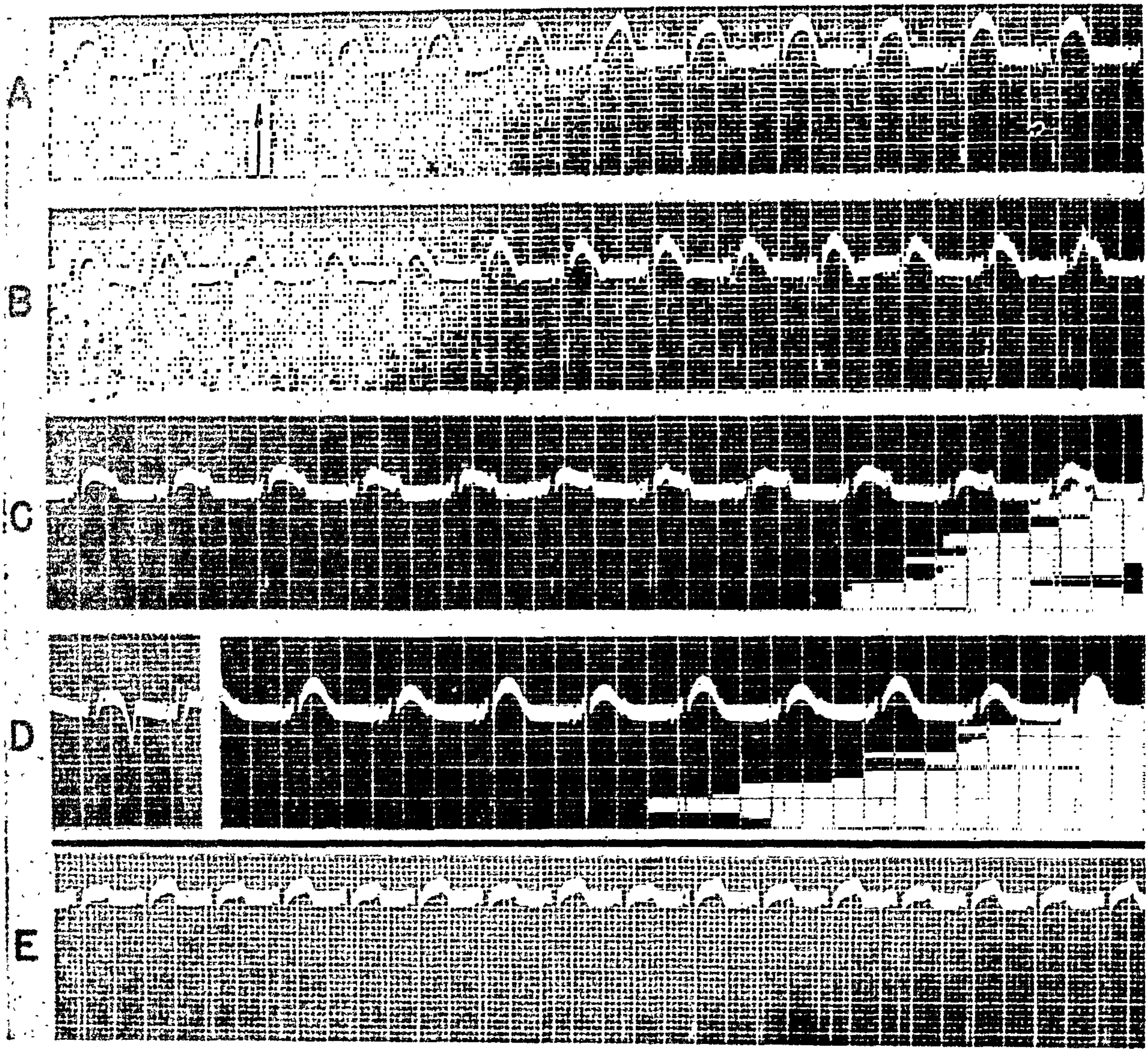

Fig. 13.—Electrical changes occurring in the right ventricular cavity and at the epicardium superjacent to an extensive transmural injury of the anterior wall of the right ventricle produced by burning an area 2.5 by 4.2 cm. on the epicardial surface with a soldering iron. Post-morten examination (Fig. 14) revealed damage through the entire thickness of the wall.

A, *B*, and *C* are from a continuous strip obtained with an exploring electrode in the right ventricular cavity subjacent to the injury. The arrow in *A* indicates time at which injury was produced. It will be seen that this extensive injury produced no change for twelve seconds. In *B*, T has become smaller and is diphasic (±). Seventy-two seconds later when *C* was taken, T has become notched. However, no S-T deviation was produced by the injury at any time.

D shows the effect of this extensive injury upon the record obtained with an exploring electrode on the epicardium over the center of injury. The first segment is the control; the second segment was taken ninety seconds after the injury was produced. Note the similarity of the epicardial record, after injury, to the intracavity tracing. Also note the appearance of an electrical alternans involving the ST-T complex. Ventricular fibrillation occurred ten minutes later.

E shows another instance of electrical alternans involving the ST-T complex, obtained in another preparation with a right intracavity electrode following extensive injury of the right side of the intraventricular septum. Discussed in text.

In another animal, the intracardiac electrode was inadvertently pushed through the apex of the right ventricle. No injury effects were noted in the right intracavity lead or in epicardial leads, even when the exploring electrode was within 2.0 mm. of the hole.

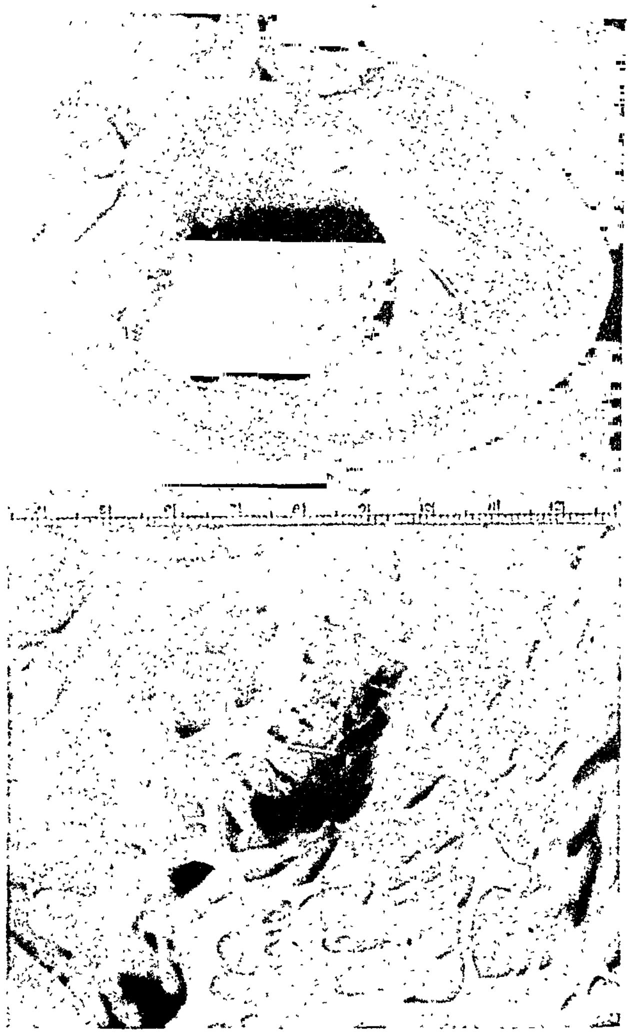

Fig. 14.—Photographs illustrating post-mortem appearance of transmural char injury of the right ventricle, the preparation from which tracings *A*, *B*, *C*, and *D* of Fig. 13 were obtained. Black area represents the charred region. Upper picture shows the epicardial surface; lower picture, the endocardial surface.

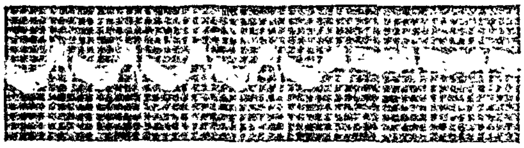

Fig. 15.—The electrical changes occurring at the endocardium superjacent to a subendocardial injury of the right atrium produced by the exploring electrode (by pressure). Electrode pressure was begun before the record was taken and was released before the third from the last beat of the record. Note that during injury the P-Q (P-T_A) segment is elevated and that following release it returns to the isoelectric level. Discussed in text.

VII. Effect of Intramural Injury on Epicardial and Intracavity Leads.—In one animal a pure intramural injury without involvement of the subendocardium or subepicardium was successfully produced in the anterior wall of the left ventricle by alcohol injection. After the needle was inserted and the position of its tip determined, a control record was taken from the superjacent epicardial surface. The minimal S-T deviation which developed subsided in less than ten minutes. Then 0.5 c.c. of 95 per cent alcohol was injected. No injury effects were found in the epicardial and intracavity leads (Fig. 17, lower right hand drawing). Autopsy confirmed the purely intramural position of the injury. In this same animal other parts (subendocardial and subepicardial) of the left ventricle were later injected with alcohol and the expected injury effects appeared. Apparently, therefore, the lack of change in purely intramural injury is to be attributed to the absence of subepicardial or subendocardial involvement.

In two other animals in which such injury was attempted, it was found, post mortem, that the injury had extended to the epicardium.

VIII. Miscellaneous Observations.—It was noted that a Q wave appeared in epicardial leads following injury only in those instances in which there was morphologic evidence at necropsy that the injury was complete and transmural. This Q wave was not found outside the area of injury.

Records made from the epicardial surface of the left ventricle while the subendocardium of the right ventricle was being injured revealed many instances of premature beats in which the peak of the R wave was relatively late. This finding is compatible with the idea that the beat originated at the site of injury. A simliar late occurrence of the peak of R was seen in premature beats recorded from the epicardium of the right ventricle during injury of the subendocardium of the left ventricle. This is interpreted in the same way.

Subepicardial injury led to a significantly longer duration of the injury effect than occurred with a similar injury to the subendocardium.[11,13] Furthermore, injury of the subepicardium produced a greater injury effect than a similar amount of injury to the subendocardium. The lesser effect and shorter duration of subendocardial injury may depend upon the constant lavage of the injured endocardium and subendocardial myocardium by the blood coursing through the heart cavities and leading to dissipation of the products of injury.[13] In clinical subendocardial injury the endocardium is usually intact, so that the injury effect would be expected to persist for a longer period of time.

It was found that the sensitivity of various parts of the endocardial surface of the ventricles in producing ventricular fibrillation varied greatly. Injury of the posterobasal part of the interventricular septum and of the papillary muscles of the left ventricle most readily led to ventricular fibrillation.

Intracavity electrodes remained in situ for eight or more hours without the formation of intracardiac thrombi. In only three of thirty-one animals was there any evidence of trauma due to the presence of the intracardiac electrodes. Localized subendocardial hemorrhage was found in these cases at the junction of the superior vena cava with the right atrium. This is attributed to the protracted irritation by the electrode rod. No change in cardiac rhythm was caused by this atrial hemorrhage.

After opening the pericardium with minimum handling of the heart, the T waves in the control record obtained with direct epicardial electrodes were found to be inverted, a phenomenon previously discussed by Pruitt and associates,[11] Smith,[12] and Byer and associates,[13] and attributed by them to the effect of cooling on repolarization. In intracavity leads the T waves were upright when the chest was opened. However, in the animals with closed chests the T waves were inverted in the right intracavity lead.

DISCUSSION

The results of these experiments can be readily explained by a logical extension of the classical membrane theory as applied to a heart immersed in an extensive conducting medium.

The classical membrane theory postulates that the atria and ventricles are each a syncytial cell bounded by a semipermeable membrane. In the resting state the cell surface is polarized with an equilibrium existing between the positive charges on the outside and the negative charges on the inside of the surface. During activation of the cell the polarized state at its surface is destroyed. This does not happen simultaneously in all parts of the cell, but develops asynchronously with a typical topographical spread. When all parts of the cell are activated the cell surface is completely depolarized and, as in the polarized state, all parts of the cell surface are at the same potential. After a brief time the polarized state is restored to the cell surface. Repolarization, like depolarization, is not simultaneous in all parts of the cell, but has a typical topographical distribution which ordinarily is different from that taking place during depolarization.

When the cell is in an extensive conducting medium it can be shown that during depolarization and repolarization a hypothetical surface at the junction between depolarized and polarized portions of the cell can adequately account for the electrical field created in the medium. The series of doublets lining this theoretical surface can depict the origin of the electrical field. The negative poles of these doublets are on the side of the surface toward the depolarized portion of the cell while the positive poles are toward the polarized portion of the cell, and the intensity of the charge on the theoretical surface is equal to the intensity of the charge on the polarized part of the cell surface. This concept, first developed by Lewis,[18] was amplified by Craib,[19] Ashman and associates,[20] Bayley,[21] and others[28] and has been most clearly ennunciated by Wilson and co-workers.[22] Further details can be obtained by reference to Wilson and co-workers[22] and to Katz.[10]

When the myocardium is injured the simplest effect is that the surface membrane in the region of injury is destroyed or depolarized. The polarized surface membrane of the uninjured part of the resting syncytial cell no longer forms a closed surface. In an extensive conducting medium an electrical field is established which can be accurately portrayed by assuming a theoretical surface at the junction between the injured and uninjured parts of the cell. The intensity of the charge on this theoretical surface is the same as that on the surface of the

uninjured part of the cell. The charges on this theoretical surface are oriented so that the negative charges face the injured part and the positive charges face the uninjured part of the cell. This would be the state of affairs during the resting period of the uninjured part of the cell. A current of injury will therefore flow during rest, having as its apparent source that aspect of the theoretical surface adjacent to the uninjured part of the cell and as its apparent sink that aspect of the theoretical surface adjacent to the injured part of the cell. This current of injury will flow as long as the uninjured part of the cell remains polarized. When the cell is completely activated and its uninjured surface is completely depolarized, the current of injury will disappear, only to reappear when the cell surface of the uninjured part begins to repolarize. This has, therefore, been called an injury current of rest. In this situation the S-T segment would not be displaced from the isoelectric level, only the T-R segment.

Other possibilities following injury have been postulated by Eyster and associates,[23,24] by Ashman and co-workers,[20] and especially by Katz and associates.[10,14] For example, the injured part of the cell may not be depolarized by injury but may become unresponsive during activation. Hence, during the resting stage of the cell no injury current will occur because all parts of the cell have the same polarized state. Thus, no injury current of rest appears. However, during activation all parts of the cell, except that which is injured, will be depolarized so that during activity a theoretical surface may again be depicted at the junction between injured and uninjured parts of the cell, with the charges so arranged that the positive charges are adjacent to the injured part and the negative charge adjacent to the uninjured part. This will give rise to an injury current of activity. In this situation there would be an S-T deviation from the isoelectric level but no T-R displacement.

Another possibility which can occur following injury[14] is that the injured region is partially depolarized and, at the same time, becomes unresponsive. Under these circumstances there would be an injury current of rest, oriented, as in the case already outlined, where the injured part of the cells was assumed to be completely depolarized, but it would be of smaller magnitude. In addition, however, there would also be an injury current of activity, oriented as in the case where the injured part of the cell was assumed to be completely polarized but unresponsive, but it too would be of smaller magnitude. In this situation there would be both an S-T displacement and an opposite T-R displacement from the isoelectric level, the magnitude of each being dependent, respectively, on the extent of depolarization of the injured part during rest and the completeness of the unresponsiveness of the injured part during activation.

In the present experiments the validity of these possibilities was clearly established both for subepicardial and subendocardial injury. The experiments were carried out with exploring electrodes on the injured part, on the superjacent uninjured part, and at distant points both in the cavities of the ventricles and on the epicardial surface of the heart. In Fig. 19,*B*, *C*, and *D*, these three possibilities are diagrammatically represented, and in Fig. 16 the actual time evolution of typical experiments, as far as S-T and T-R displacement are concerned, are shown. For example, it was found that in records from the injured area produced

by the endocardial pressure injury, instances were found in which the T-R segment showed marked depression with the S-T segment showing little elevation from the isoelectric line. In other experiments, equal displacement in opposite directions of the S-T and T-R segments appeared, and in some experiments the S-T displacement was marked while the opposite T-R segment displacement was slight.

In previous reports from this laboratory,[10,14] another effect of injury was postulated: an effect upon the repolarization process. This was called the injury current of repolarization. In such circumstances, whether or not the injured part of the cell was partially depolarized, it was assumed that injury could retard the repolarization of the injured part of the cell, provided that it was at least partially responsive. The T waves following injury were accounted for in this way. In the present experiments, the injury current of repolarization ordinarily appeared at a different time or in a different location from that of the injury current of rest and/or activity, confirming the earlier work of this laboratory.[14] This injury current of repolarization appeared not only with subepicardial injury but with subendocardial injury as well. The well-established fact that "coronary" T waves, representing, we believe, injury currents of repolarization, occur later than injury currents of rest and/or activity was clearly confirmed in these experiments. In addition, several instances were found in which the injury current of repolarization preceded the injury current of activity and/or rest. This confirms the observation of Bayley and co-workers[25] that "coronary" T waves may precede the S-T deviations. However, our interpretation of this phenomenon differs from that offered by Bayley and associates.

Obviously, when the injured part of the cell is completely depolarized or unresponsive it will not contribute to the electrical field created during activation. This lack of response of the injured part is responsible for the alteration of the QRS complex found with injury. Our present experiments have confirmed the presence of such QRS changes. When, however, the injured region is not completely depolarized and remains responsive, it is possible that injury may lead to prolongation of the depolarization in the injured area when it is activated and thus produce prolongation of QRS. Such prolonged QRS complexes during injury, with the associated and expected alterations in the S-T segment and T wave, were found on several occasions following subendocardial injury in regions confined to the neighborhood of the injury. It appears, therefore, that in these experiments we have demonstrated injury effects during depolarization which, by retarding the process of depolarization in the region of injury, lead to prolongation of QRS limited to exploring electrodes in the immediate neighborhood of injury. We have called this *local focal intraventricular block*. In the presence of extensive areas of injury this local focal intraventricular block might possibly lead to prolongation of QRS, even in more distant leads.

The direction of the displacement of the S-T segment and T-R segment found in these experiments can be explained logically on the spatial orientation of the exploring electrode in relation to the region injured. While no precisely quantitative orientation between the electrode and the theoretical charged surface postulated at the junction of the injured and uninjured areas can be made

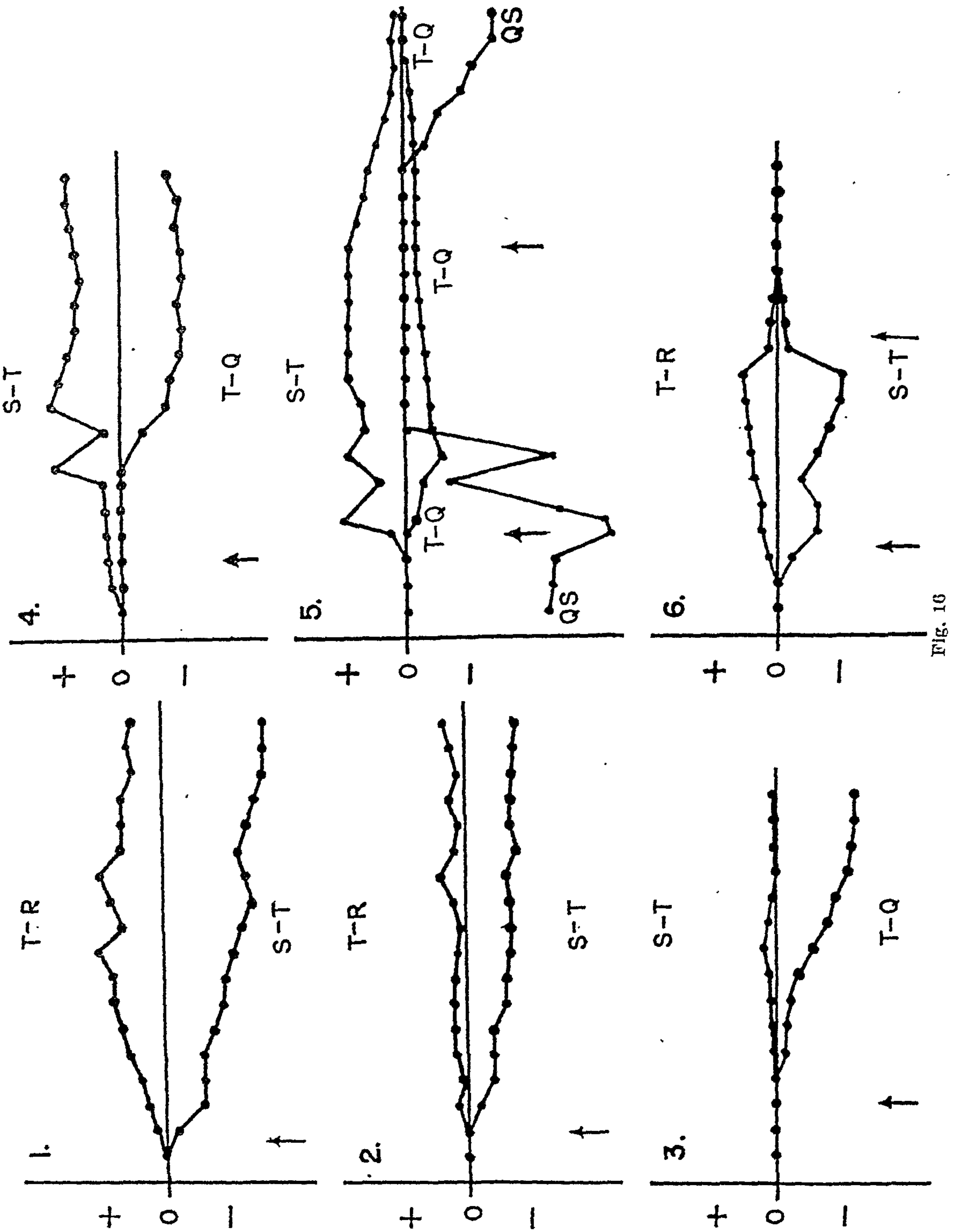

Fig. 16.—Six charts constructed as in Fig. 2 of a previous communication[14] to show the extent and time course of the S-T and T-R (T-Q) displacements following injury in the several experiments. In each case, the arrow indicates when injury was induced. In Charts *5* and *6* two arrows are shown, the second one indicating the time of release of compression injury; these charts thus show also the effects of recovery from injury. The S-T and T-R (T-Q) displacements are recorded for each beat from continuous records plotted in millimeters against time. The cycle lengths of Graphs *1* to *6* are

(*Legend continued on opposite page.*)

on the basis of the solid angle subtended from the exploring electrode to the theoretical surface, nevertheless, the directional changes found show no exception from the expected rules, other than that found when the exploring electrode was close to the edge of the injured region.

The true displacement caused by injury of the S-T and T-R segments can only be obtained by a continuous record while injury is produced. In this situation the reference level for displacement is the isoelectric level found before injury is produced. Ordinary records taken at intervals after injury will not reveal whether it is the S-T, or T-R, or both, which have been displaced. Under these circumstances, the T-R displacement, as well as other constant currents, is neutralized by the introduction of oppositely directed compensatory currents, and there is no way of distinguishing the injury current of rest from these other constant currents. Hence, the T-R displacement will remain unrecognized as such and will be manifest as an opposite displacement of S-T, since during complete depolarization the injury current of rest is no longer flowing and the introduced compensatory current is unbalanced. The S-T displacement is judged from the T-R level which in interrupted records is taken as the isoelectric level.

With the exception of the case of the electrode close to the edge of injury, which will be discussed later, the rest of the findings follow simple rules. If a plane is constructed parallel to the surface of the heart upon which the injury was produced so as to fall on the junction of the injured and uninjured regions, then all points on the side containing the injured area will show an elevated S-T segment and/or a depressed T-R segment while all points on the opposite side of this plane will show the reverse deviation of the S-T and T-R segments. The data shown in the actual experiments, notably Figs. 7, 8, 9, 10, and 11, as well as the summary charts in Fig. 17, will show this to be true. This is summarized schematically in Fig. 18. The foregoing proposition was found to pertain both to subepicardial injury and to subendocardial injury. Strikingly enough, the effects on the S-T segment and T-R segment of subendocardial and subepicardial injury of the same part of the wall of the ventricle gave exactly opposite

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respectively, 0.34, 0.36, 0.30, 0.28, 0.52, and 0.28 second. The zero line represents the isopotential level at the site of the exploring electrode determined before injury was induced.

In Chart 1, the injury was subepicardial and located on the posterior wall of the left ventricle (topical potassium chloride) and the exploring electrode was on the epicardium of the anterior wall of this ventricle. The S-T depression produced was greater than the T-R elevation.

In Chart 2, the injury was a subepicardial one on the lateral apical region of the left ventricle (topical potassium chloride) and the exploring electrode was in the right ventricular cavity. The S-T depression produced was more marked than the T-R elevation.

In Chart 3, the injury was a subendocardial one on the anterior wall of the right ventricle (pressure electrode) and the exploring electrode was therefore over the injury. No significant S-T deviation was produced but a definite T-R (T-Q) depression developed.

In Chart 4, the experimental conditions were the same as in Chart 3. Here, however, the S-T elevation produced was of the same extent as the T-R (T-Q) depression.

In Chart 5, the experimental conditions were the same as in Chart 3. Here, however, the S-T elevation produced was greater in extent than the T-R (T-Q) depression. A monophasic ventricular curve developed and QS disappeared, as indicated. With release of the pressure, the S-T, T-R (T-Q), and QS tended to return to their control values.

In Chart 6, the injury was located and produced as in Charts 3, 4, and 5. However, the exploring electrode in this instance was located on the epicardium superjacent to the subendocardial injury. The direction of S-T and T-R displacement is the reverse of that occurring in the preceding three graphs. The S-T depression is a little greater than the T-R elevation. Complete recovery occurred within two beats following release of the pressure on the endocardium. Discussed in text.

effects on exploring electrodes, whether these were in the cavities of the heart, on the adjacent or distant epicardial surfaces, or on the adjacent endocardial surface. Furthermore, subendocardial injury on the right side of the septum gave rise to effects in intracavity and epicardial exploring electrodes opposite to those obtained with injury to the left side of interventricular septum. When the exploring electrode came to lie in the projection of the plane between the injured and uninjured regions parallel to the wall of the ventricle involved, then

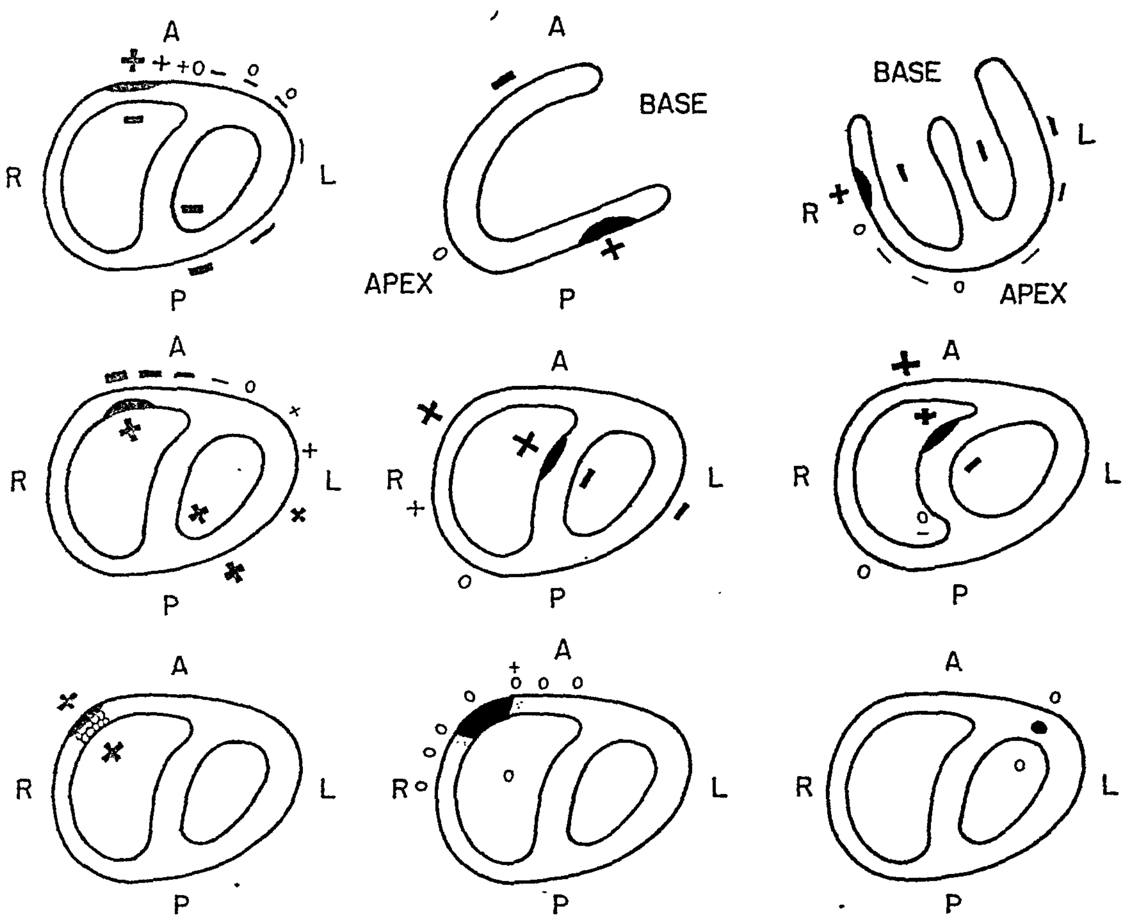

Fig. 17.—Diagrammatic representation of the effect of injury in various locations on the S-T displacement. The blackened area in each of the nine figures locates the injured area. Stippling indicates regions of injury intermingled with uninjured regions. Network indicates extension of hemorrhagic regions beyond injury. Plus (+) means S-T elevation; zero (0), isoelectric S-T; minus (—), S-T depression; the thickness of plus and minus signs gives an index of the relative magnitudes of the S-T deviations. *A* is anterior; *P*, posterior; *R*, right; and *L*, left. Discussed in text.

no S-T or T-R displacement occurred. This was true for subepicardial and subendocardial injury and was true whether the latter was of the interventricular septum or the outer wall of the ventricles. Furthermore, the magnitudes of the S-T and T-R deviations reached their maxima when the exploring electrode distant from the injury was situated at an angle normal to the plane of the injured ventricle. Wilson and associates[22] have stated the principle of this concept in these words: "If the injured fiber is immersed in an infinite medium, the potential of any point *P* within the medium will be ϕ *W* where *W* is the solid angle sub-

tended by the region of injury. If the medium is transparent and the muscle opaque, the potential of all points from which the injured region is visible will be negative, and that of all other points will be positive (during diastole)."

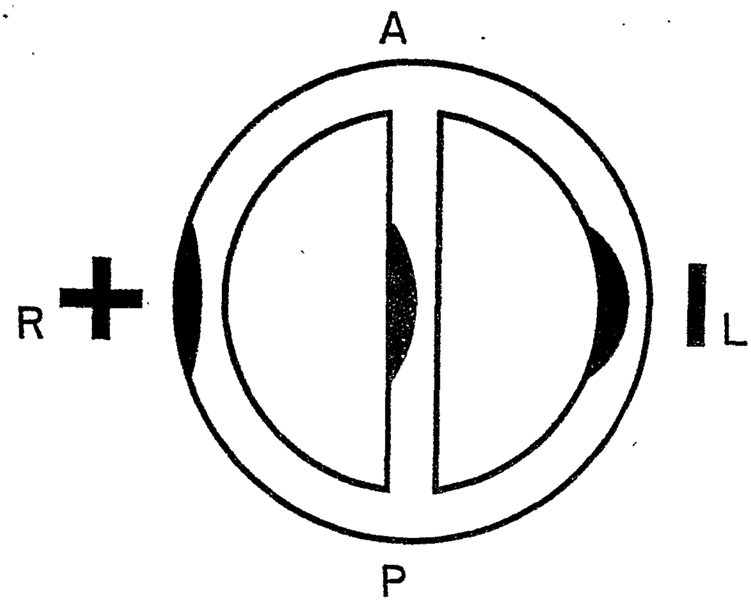

Fig. 18.—Schematic recapitulation of findings. Conventions as in Fig. 17. Shown are subepicardial injury of the right lateral wall, subendocardial injury of the right side of septum, and subendocardial injury of the left lateral wall. If the figure is rotated 180° and P and A, and R and L are reversed, the effect of three other injury locations will be illustrated, namely, of the subepicardium of the left lateral wall, of the subendocardium of the left side of the septum, and of the right lateral wall. Discussed in text.

To illustrate this point (see Fig. 18), upward displacement of the S-T segment will occur when the exploring electrode overlies an area of subepicardial injury, when the electrode is placed in the cavity or on the epicardial surface of the ventricle whose interventricular septal subendocardium is injured, or when the exploring electrode is within the heart cavities or on the epicardial surface of the wall of the ventricle opposite to that containing a subendocardial injury. Conversely, downward displacement of the S-T segment will occur when the exploring electrode is on the epicardial surface overlying a subendocardial injury, when the exploring electrode is within the cavity or on the epicardial surface of the ventricle opposite to that containing a subendocardial injury of the interventricular septum, or when the exploring electrode is on the epicardium of the wall of the ventricle opposite to that containing a subepicardial injury.

The situation may be summarized differently. A vector may be used to represent the *effect* of injury. It would appear to be directed at right angles to the surface injured and have its negative and positive poles arranged so that during the activated state the former would appear to be on the side having the junction of injured and uninjured regions and the latter, the junction of injury with the surface of the heart, whether this be epicardium or endocardium. In this way S-T elevation will be present on that side of the injury which surfaces on the heart and S-T depression on that side of the injury which adjoins uninjured tissue, since (by construction) an electrode which is in a relatively positive

electric field will record an upward deflection and an electrode which is in a relatively negative electrical field will record a downward deflection. The situation for an injury current of activity is self-evident. In the case of an injury current of rest, this orientation of the vector comes about because the injury current is neutralized and hence, only the compensatory current is recorded when during the completely activated state the injury current no longer is flowing.

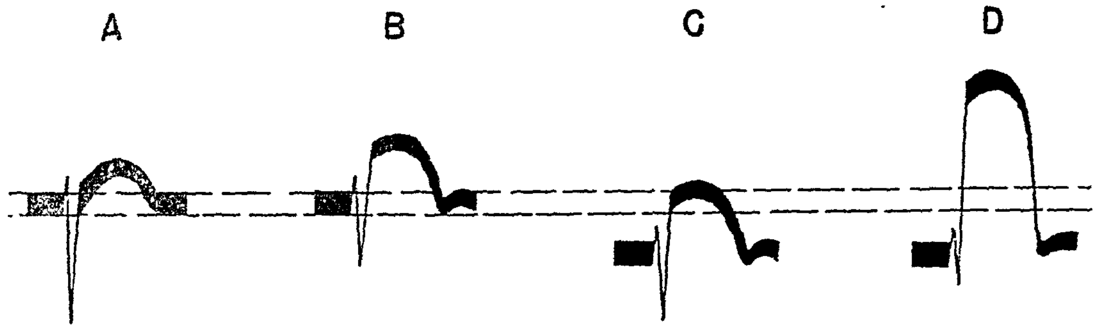

Fig. 19.—Schematic representation of the three types of injury effects found in leading from a subendocardial injured area produced by a pressure electrode. These are similar to those described for subepicardial injury.[14] The dotted line represents the isoelectric level determined from the control record, *A*. This control record is from the tip of the right ventricular cavity. *B*, *C*, and *D* represent curves after injury. In all, the S wave becomes smaller. In *B*, the development of an injury current of activity is depicted; this causes the S-T segment to be elevated. In *C*, the development of an injury current of rest is depicted; this causes the T-R (T-Q) segment to be depressed. In *D*, the development of both an injury current of rest and an injury current of activity is depicted; this causes both elevation of S-T and depression of T-R (T-Q). Such changes are obtained only in continuous records, started before injury is made; the control record serves to locate the isoelectric level from which S-T and T-R (T-Q) deviations can be judged. When a large symmetrical T wave appears, it is inverted; it represents an injury current of repolarization. Discussed in text.

These simple rules must be modified when the exploring electrode is in the neighboring epicardial surface surrounding a subepicardial injury. Here the theoretical surface between injured and uninjured areas cannot be considered as a single unit but must be broken down into its component parts. With a subepicardial injury that is extensive, most of the theoretical surface between injured and uninjured surfaces will be parallel to the surface of the heart, but at its edges the theoretical surface will come to lie progressively more perpendicular to the heart surface. When the exploring electrode is in the neighborhood of the injury it will be at an unequal distance from various parts of the theoretical surface between injured and uninjured areas. Hence, the more distant part of this surface will have a significantly less marked effect, depending upon the extent of the injury. As a rough approximation it may be considered that only that part of the theoretical surface close to the electrode affects its potential when the electrode is near one edge of the injury; this might be called an intrinsic effect. Take the simplest situation, that of a case with only injury current of rest. The part of the theoretical surface close to the electrode is at right angles to the surface of the heart with its positive charge in the uninjured side and its negative charge on the injured side. When the exploring electrode is over the injured area the S-T segment will be displaced upward, but as the exploring electrode is moved over to the uninjured region, even though it be on the same wall as

that which has been injured, the S-T segment becomes isoelectric, and in more distant regions on the same wall, it becomes depressed. This confirms the original observation of Wilson and co-workers.[22] Thus, in a complete experiment such as is diagrammatically depicted in the upper right-hand diagram of Fig. 17, there will be two zones of isoelectric S-T segments on the epicardial surface of the heart: The first, in the immediate neighborhood of the injured area, is due to the predominant effect of that part of the theoretical surface which is closest to the exploring electrode; the second, occurring while the electrode is moved from the wall upon which the injury is located to the opposite wall, is due to spatial orientation of the exploring electrode to the major aspect of the theoretical surface.

It is significant that the effects of subendocardial injury on superjacent endocardial or intracavity electrodes are remarkably similar to those of subepicardial injury on superjacent epicardial electrodes. This is not unexpected since injury in either location causes similar effects. The use of the endocardial pressure electrodes and the intracavity catheter electrodes in our experiments has helped to clarify the role of the subendocardial myocardium in the genesis of the electrocardiogram. There can be no question from our results that the subendocardium is not electrically silent, as suggested by some investigators.[4,11]

Our experience with transmural injury shows that less change occurred in the subjacent intracavity electrode than with slight superficial subepicardial injury in other experiments. Total death occurred in these transmural injuries as demonstrated by the tracings taken with the exploring electrode on the epicardial surface at the center of the injury. The record so obtained was almost identical with that obtained from within the cavity, suggesting, following Wilson and associates,[26] that a new "window" has been opened into the cavity of the heart. In clinical myocardial infarction, the QS obtained in chest leads lying over the area of infarction has been explained in similar fashion. The argument is based on the fact that a QS is frequently observed when the chest electrode is at the C_1 position and in the V_R lead. The exploring electrodes in these two situations have a spatial orientation which permits them "to look through the normal window of the ventricle," the A-V opening, and so pick up the same type of record as can be obtained within the cavities of the heart during activation. If this argument is correct, then the complete transmural injury produces a tubular "hole" in the ventricle with negative charges on its inside and positive charges on its outside. On both the endocardial and epicardial surfaces, these charges would tend to neutralize each other and hence no S-T deviation might be expected. If the transmural injury were larger, then S-T elevation might be expected on the epicardial surface for two reasons: (1) The injured area would be conical with its greater diameter on the epicardial surface so that the theoretical surfaces would face outward; and (2) when the exploring electrode is closer to one edge than the other, that edge will have a dominant influence as in the case of a subepicardial injury.

With incomplete transmural injury, upward S-T displacement was recorded both with a subjacent intracavity electrode and with an epicardial electrode over the injury. The epicardial effects can be explained as being due to a

laminar subepicardial injury, while the intracavity effects can be explained by discrete subendocardial injury.

When a purely intramural injury was produced which did not surface on the epicardium or endocardium no injury currents were obtained. This is not unexpected since the theoretical surface between injured and uninjured areas would constitute a complete sphere or at least a completely enclosing three-dimensional surface and the charges on this surface would neutralize each other completely.

The results of our experiments are for the most part in accord with those obtained in the excellent study of Wolferth and co-workers.[3] The suggestion made by Wolferth and his colleagues that the S-T displacement can be classified as *primary* and *secondary* is in our opinion neither valid nor necessary. We have shown that the direction of the S-T displacement depended purely upon the spatial orientation of the exploring electrode in relation to the theoretical surface between injured and uninjured areas, except that when the exploring electrode is near the edge of the injury, it will depend upon its relationship to the theoretical surface closest to it. This has been discussed in detail and various combinations of injury location and exploring electrode position confirming our explanation have been amply illustrated.

The results of our experiments may have a bearing on the interpretation of the S-T segment displacement in precordial leads in man. Thus, with an anterolateral infarct, marked S-T depression may be found in the C_2 position and increasing S-T elevation may appear in the C_4, C_5, and C_6 positions overlying the injury. This is analogous to electrodes placed, respectively, outside and over a subepicardial injury in our experiments. Again, with an anteroseptal infarct extending to the left side of the interventricular septum, S-T depression may appear in the C_1 and C_2 positions with S-T elevation in the C_4, C_5, and C_6 positions. This is analogous to subendocardial injury of the anterior wall of the left ventricle. Furthermore, the realization that S-T elevation in precordial leads can occur as a result of subendocardial injury of the wall of the heart may explain occasionally atypical posterior wall infarctions which produce typical changes in the limb leads but unexpected S-T elevation in one or more of the precordial leads despite the fact that the infarct does not extend anteriorly. We are convinced that other situations with atypical combinations of S-T changes in precordial leads may be explained along the lines developed in this report.

Our present study offers a reasonable explanation for the contradictory effects reported previously by this laboratory[27] following injury to the various walls of the left and right ventricles. It is possible that during these early experiments the injury produced was in some instances epicardial; in others, endocardial; and in still others, purely intramural. Unfortunately, the location of injury to the epicardium and endocardium was not noted at that time. It is not only the location of the injury on a certain wall of the ventricle which is important but also the fact of whether it is subendocardial, subepicardial, intramural, or transmural.

SUMMARY

1. When an exploring electrode was placed on an area of subepicardial injury (the indifferent electrode being on the left hind paw), an upward S-T displacement occurred; a downward S-T displacement was found when the exploring electrode was placed on the marginal zone surrounding the area of injury. When a contact wick exploring electrode was moved from the area of injury to surrounding uninvolved tissue and continuous records made, a narrow transitional zone was found in which the S-T segment was isoelectric. In regions removed from the area of injury an exploring electrode showed the S-T segment to be slightly depressed or isoelectric in the surrounding epicardium on the same side as the subepicardial injury, depending upon the extent of the injury. When the exploring electrode was on the epicardium of the wall opposite to that injured, downward S-T displacement occurred which was maximal when the exploring electrode was on the axis normal to and intersecting the center of the plane of the area of injury. In passing from the wall injured to the opposite wall a zone in which the S-T segment was isoelectric was found.

2. While the area of upward S-T displacement was confined to the area of injury at the time of injury, with the passage of time S-T elevation extended to surrounding regions on the same wall. At all times, however, the S-T segment displacement was greatest over the area of epicardial injury. The spread of injury effects was uneven. The S-T displacement in equidistant points from the injured area were not of the same magnitude nor did they appear at the same time. The injury effects were usually greater in areas toward the base of the heart.

3. The electrical effects produced by subendocardial pressure or scrape injury on endocardial or intracavity exploring electrodes were similar to those produced over the epicardial surface of a subepicardial injury. These included S-T elevation and T-R depression; monophasic ventricular curves were found. Continuous records over the subendocardial injury, made while the injury was produced, revealed three types of injury effects on the S-T and T-R segments: (1) downward displacement of T-R with no or slight upward displacement of S-T, that is, primarily an injury current of rest; (2) slight downward displacement of T-R and marked upward displacement of S-T, that is, primarily an injury current of activity; and (3) most commonly, almost equal downward displacement of T-R and upward displacement of S-T, that is, injury currents of both rest and activity. These changes in S-T and T-R segments disappeared in parallel fashion on recovery from the injury.

4. The production of S-T segment elevation at any part of the epicardial surface of the heart by various methods of injury of the subepicardium was accompanied by S-T segment depression in leads from the cavities of the heart. This pertained also to the atria.

5. Localized injury of the subendocardium (exclusive of the interventricular septum) resulted in S-T elevation in leads from the heart cavities. Epicardial electrodes directly superjacent to the subendocardial injury showed S-T depression. Leads made with epicardial electrodes at distant points on the wall injured showed slightly depressed or isoelectric S-T segments. Epicardial leads taken at points on the wall opposite to that injured showed S-T elevation.

6. Subendocardial injury of one side of the interventricular septum resulted in S-T segment elevation in leads from the ipsilateral cavity and the epicardium of the ipsilateral free wall, and S-T segment depression in leads from the contralateral cavity and the epicardium of the contralateral free wall. The importance of spatial orientation of the electrode to the area of injury was demonstrated by the absence of S-T segment displacement in an intracavity electrode which was located in the tip of the right ventricle, where the upper anterior part of the left side of the interventricular septum was injured by scraping. The septum bulged convexly into the right ventricle, so that the electrode in the tip of the right ventricle lay in a plane which was the extension of that of the major surface of the subendocardial injury.

7. Incomplete transmural injury of the ventricles produced by cauterization resulted in S-T segment elevation in electrodes on the epicardium over this area and within the underlying cavity. However, instantaneous complete transmural injury produced by charring a large area of the anterior wall of the right ventricle produced minimal changes in the S-T segment and QS of the subjacent right intracavity electrode, and the epicardial electrode over the center of the charred area yielded tracings identical to those obtained from the cavity.

8. Isolated intramural injury produced no detectable injury effects in superjacent epicardial electrodes.

9. It was found that elevation of the S-T segment appeared:

(A) When the exploring electrode was placed on the epicardium immediately superjacent to subepicardial injury.

(B) When the epicardial electrode was placed on the ventricular wall opposite to that containing a subendocardial injury. The S-T elevation was greatest when the electrode was approximately 180 degrees away, that is, on the axis perpendicular to and intersecting the center of the plane of the area of injury.

(C) When the epicardial electrode was placed on the lateral wall of the ventricle in the cavity of which a subendocardial injury of the interventricular septum surfaced.

(D) When endocardial and intracavity exploring electrodes were used after injury of the subendocardium of the outer walls of the ventricles and after injury of the ipsilateral side of the interventricular septum.

10. It was found that depression of the S-T segment occurred:

(A) When the epicardial exploring electrode was placed outside of the area of subepicardial injury. However, two transition zones with isoelectric S-T segments were found. One was near the injured area and the other occurred in passing from the wall injured to the opposite one.

(B) When the epicardial exploring electrode was placed superjacent to subendocardial injury.

(C) When intracavity electrodes were used following injury of the subepicardial surface of any part of the ventricles.

(D) When intracavity electrodes were used following injury of the contralateral side of the interventricular septum.

11. Injury also produced T-wave changes. Usually these developed while the S-T deviations were receding or after they had disappeared. Occasionally, the T-wave changes occurred transiently before the S-T deviations developed. These observations confirm the existence of injury currents of repolarization. Injury of the subendocardium, on rare occasions, produced QRS prolongation in the regions of injury; local focal intraventricular block. This is interpreted as evidence of an injury effect on depolarization.

12. The relation of these results to the modern concept of injury effects in an extensive conducting medium are discussed. The various types of injury effects are developed: namely, injury current of rest, injury current of activity, injury current of repolarization, and injury effect of depolarization; their demonstration by these experiments is shown. The spatial relation of the exploring electrode to a theoretical surface at the junction of the injured and uninjured areas is used to account adequately for the findings.

13. The present results confirm and extend previous observations of this laboratory.

14. The practical value of these observations is considered.

We are indebted to Mrs. B. Lendrum for her assistance in the preliminary experiments.

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CIRCULATORY RESPONSES TO SPINAL AND CAUDAL ANESTHESIA IN HYPERTENSION: RELATION TO THE EFFECT OF SYMPATHECTOMY

I. Effect on Arterial Pressure

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THE effects of high spinal anesthesia upon arterial pressure and renal circulation of patients suffering from essential hypertension have been described in brief.[1] In most of the patients, induction of anesthesia resulted in a decrease in arterial pressure. On the assumption that the effects on the circulation of high spinal anesthesia were in large measure similar to those resulting from sympathectomy (lumbodorsal sympathectomy and ganglionectomy), we suggested that the response of arterial pressure to high spinal anesthesia might aid in selecting patients for this operation. Caudal anesthesia differs from spinal anesthesia in that it does not paralyze the nerve supply of voluntary muscle, although it does affect preganglionic sympathetic fibers, so that the denervation is more like that of sympathectomy than is that induced by spinal anesthesia. Such considerations led Russek and co-workers[2,3] to the observation that high caudal anesthesia caused a reduction in blood pressure in many patients suffering from hypertension which paralleled the effect on arterial pressure of subsequent surgical sympathectomy. They recommended measurement of arterial pressures during high caudal anesthesia as a guide to the selection of patients for sympathectomy.

The purpose of this report is to examine the relationship between the effect on arterial pressure of high spinal or caudal anesthesia and the effect of subsequent sympathectomy by the procedure of Smithwick.[4]

PROCEDURES

Preoperative and postoperative studies were made in forty-three patients. Spinal anesthesia was induced in twenty-five of these and caudal anesthesia in eighteen.† The brachial blood pressure of each patient was measured in the supine position twice daily during the four to ten days of hospitalization which preceded operation. The levels taken as controls for each patient in this study were the arithmetic means of these readings.

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Spinal anesthesia was induced by intrathecal injection of 180 mg. of Spinocain. In all cases, there was anesthesia extending at least to the level of the sixth thoracic spinal segment. Blood pressure was recorded each minute until constant levels were observed. The lowest value was accepted as representing the maximum effect of spinal anesthesia on the blood pressure.

Caudal anesthesia was given by placing a malleable needle into the caudal canal and slowly introducing enough 1.5 per cent Metycaine solution to induce anesthesia up to at least the level of the sixth dorsal spinal segment. The lowest blood pressure level observed during the period of anesthesia was recorded as representing the effect of this procedure upon arterial pressure.

The effect of operation upon blood pressure was evaluated by comparing control blood pressure with measurements made in the supine position two weeks, three months, and six to eight months after operation.

RESULTS

Comparison of Blood Pressure Reduction by Spinal Anesthesia With That Which Followed Lumbodorsal Sympathectomy (Table I).—Spinal anesthesia, which extended to the nipple line, reduced the blood pressure of twenty (80 per cent) of the twenty-five patients to or below 140/90. In two patients, marked reductions of arterial pressure to 145/85 and 155/105 were observed. In three patients, the control levels of 178/138 and 185/140 were not changed by anesthesia.

Two weeks after lumbodorsal sympathectomy, ten of the twenty-five patients exhibited blood pressure levels that differed only slightly from the control values. Three months after operation the degree of hypertension in sixteen cases was not greatly changed from that observed before operation. Six or more months postoperatively, only six patients (24 per cent) had normal blood pressures. It is interesting that five of these six patients were among those whose blood pressures fell to normal after spinal anesthesia, and the other had a blood pressure drop from 190/120 to 155/105.

Reduction of Blood Pressure Induced by Caudal Anesthesia Compared With That Following Lumbodorsal Sympathectomy.—Caudal anesthesia which produced sensory paralysis to the level of the sixth dorsal spinal segment reduced the blood pressure of twelve of eighteen (67 per cent) hypertensive patients to normal levels. Five of the remaining six persons showed blood pressure falls of 20 mm. Hg or more, systolic or diastolic or both (Table II). The other patient showed no change in blood pressure. Two weeks after surgery twelve of these eighteen patients exhibited hypertension similar to that observed before operation. Four had normal blood pressures, and two showed hypertension of a lesser degree than that present before operation. Only four of the eighteen patients (22 per cent) had normal blood pressure levels measured in the supine position three to eighteen months after operation. All of these four patients had normal blood pressure

Table I. Comparison of Effects of Spinal Anesthesia and Sympathectomy on the Blood Pressures of Hypertensive Patients

No.	Age	Sex	Control B.P. mm. Hg	B.P. mm. Hg after spinal anesthesia	2 weeks after operation	3 mo. after operation	6 or more mo. after operation	Mo. of observation
1	43	M	185/105	100/80	180/105	162/110	246/134	21
2	36	F	150/110	130/86	160/90	150/110	170/110	20
3	49	F	180/90	145/85	180/90	150/100	180/120	17
4	34	F	220/140	95/75	170/110	190/120	240/140	16
5	36	M	188/120	180/140	185/110	160/120	174/128	10
6	44	M	210/120	150/95	140/95	196/140	264/170	11 Died of cerebral hem.
7	33	F	170/110	170/138	180/120	150/110	150/110	17
8	43	F	220/120	65/40	210/110	180/110	195/125	7
9	33	F	180/120	120/80	135/90	156/114	180/130	21
10	40	F	180/100	90/65	130/80	180/120	190/120	27
11	47	M	190/130	120/80	190/125	170/120	210/140	12
12	35	M	190/120	110/60	190/122	206/120	180/110	8
13	30	F	175/100	100/70	110/60	150/96	156/100	6
14	44	M	210/130	180/130	180/115	220/160	240/140	12
15	37	F	170/120	110/80	135/95	160/110	160/120	21
16	37	F	150/100	115/70	140/90	150/84	196/110	17 Died of coronary thrombosis
17	32	M	160/105	100/65	130/90	150/108	150/102	17
18	39	M	160/100	75/50	145/95	160/104	155/115	10
19	28	M	180/130	90/30	120/85	120/92	146/100	26
20	34	F	200/140	120/90	162/115	120/92	130/84	14
21	26	F	190/120	155/105	135/88	114/80	114/80	19 Ulcerative colitis
22	34	F	170/105	115/78	140/80	110/70	144/84	28
23	30	F	160/115	95/65	140/90	165/114	138/86	12
24	31	F	190/125	100/88	175/100	130/84	136/90	20
25	41	M	175/105	120/80	140/90	120/90	115/70	12

Table II. Comparison of Effects of Caudal Anesthesia and Sympathectomy on the Blood Pressures of Hypertensive Patients

No.	Age	Sex	Control B.P. mm. Hg	B.P. mm. Hg after caudal anesthesia	2 weeks after operation	3 mo. after operation	6 or more mo. after operation	Mo. of observation
1	37	F	160/100	120/80	150/110	184/120	180/120	7
2	32	F	150/110	100/76	160/110	150/110	150/110	12
3	45	F	160/90	100/60	160/100	190/110	210/110	19
4	35	F	160/110	132/86	180/120	190/130		3
5	47	M	176/110	100/70	135/90	155/105	176/120	13
6	25	M	210/120	170/130	140/100	140/90	210/130	15
7	36	F	180/110	160/110	150/100	180/130	196/120	20
8	44	F	200/130	100/80	205/138	202/140	200/130	12
9	48	F	170/105	156/100	180/100	180/100	190/120	6
10	39	F	190/120	190/120	170/120	190/120	190/120	6
11	37	F	175/114	158/108	140/90	160/110	170/110	7
12	36	F	168/100	140/90	175/105	158/100	160/100	20
13	45	M	190/130	170/110	160/110	230/145	216/130	18
14	40	F	150/90	136/96	135/95	140/98	166/96	5
15	42	F	200/130	100/62	200/130	124/80	144/90	14
16	41	M	145/100	125/75	140/100	110/88	110/88	12
17	43	M	150/90	145/90	150/94	108/84	140/90	14
18	39	M	180/110	145/90	140/90	126/90	130/86	12

levels after caudal anesthesia, as did one of those whose pressure was appreciably reduced below control values after operation. The anesthesia reduced the pressure of the remaining patient to the same degree as did the operation, 210/120 to 170/120.

DISCUSSION

Since the effects on arterial pressure of spinal and caudal anesthesia in hypertensive patients are the same, observations on the two groups are discussed together.

Sympathectomy has at long last become an accepted procedure for the treatment of essential hypertension. The condition of many patients is favorably affected by operation. In our observations, which extend over thirteen years, the majority of patients experience subjective improvement. A minority of about 25 per cent show a sustained reduction of arterial pressure as measured in the supine position. In these latter the benefit of operation is indisputable. Others show a lessening of the severity of vascular disease in spite of continued hypertension.

Clearly the value of surgery in the treatment of hypertension would be enhanced if it were possible to select those patients whose blood pressure could be reduced or those in whom the progress of disease could be arrested. Although many methods of selection have been proposed, none has proved satisfactory. It is unfortunate but true that no single test has yet been found which allows accurate selection. The situation has not changed materially since 1938 when we selected largely at random and came to the pragmatic conclusion that patients with early essential hypertension and with early malignant hypertension had the best chance of obtaining a good result.[5] Occasionally those with advancing essential hypertension also received significant objective benefit.

Spinal and caudal anesthesia have the theoretical advantage over other tests in that their effects on the circulation depend at least in part on the mechanisms affected by sympathectomy. A parallelism of effects on arterial pressure might therefore have been expected. That this is true in some degree is apparent from the fact that ten of the twelve patients whose pressures were normal after operation had attained normal levels during anesthesia and the other two had experienced appreciable falls. However, response of arterial tension to anesthesia parallels the operative result in only one-third of our observations. Twenty-six patients who showed little or no effect from operation had shown a decrease of pressure during anesthesia.

This experience differs from that of Russek and co-workers[3] who found an association between the effect of caudal anesthesia and that of sympathectomy in eleven of twelve observations. The discrepancy may depend upon the number of our observations as compared with theirs. On the other hand, the suggestion is confirmed that those patients who respond unfavorably to preoperative block of the sympathetic fibers by anesthetic agents also respond poorly to operation. Thus, the blood pressure response to spinal and caudal anesthesia has no more than negative value in predicting the end result of sympathectomy.

There remains to be considered why the arterial tension may be greatly decreased by spinal or caudal anesthesia and still persist at preoperative levels when observed weeks or months after operation. In this connection, it should be noted that blood pressure is decreased after operation in nearly every hypertensive patient for periods of hours or days. In a few it persists at a low level, but in most it returns to a level approximating that existing before operation. It may be that the immediate postoperative decrease of pressure corresponds to that seen under anesthesia. The mechanism of this change is considered in a following paper.[6]

SUMMARY

The effects of caudal and spinal anesthesia on arterial pressure in hypertension are similar despite the fact that in the former, voluntary muscles are not paralyzed. During anesthesia marked decreases in pressure were observed in forty of the forty-three patients. Blood pressure was persistently decreased by lumbodorsal sympathectomy and ganglionectomy in twelve of these patients. The three patients whose arterial pressures were not decreased by anesthesia were similarly unaffected by operation.

It is concluded that the blood pressure response to spinal and caudal anesthesia has no more than negative value in the selection of patients for sympathectomy. The discrepancy between the effects on arterial pressure of spinal or caudal anesthesia and sympathectomy may be due to the great difference in time during which the effects are observed or to a difference in the denervation which each of them causes.

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CIRCULATORY RESPONSES TO SPINAL AND CAUDAL ANESTHESIA IN HYPERTENSION: RELATION TO THE EFFECT OF SYMPATHECTOMY

II. Effect on Renal Function

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SPINAL anesthesia in normal subjects causes moderate arterial hypotension (average arterial pressure, 86 mm. Hg) with little change in the levels of renal blood flow and glomerular filtration rate.[1] An analysis of these data indicates that renal vascular resistance is decreased during the period of anesthesia and hypotension.[2] In contrast, the urea clearance of hypertensive subjects is often reduced during hypotension caused by high spinal anesthesia.[3] This change is the result of decreased renal blood flow and glomerular filtration.[4] These observations seem to suggest that there is an essential qualitative difference between the renal vascular responses of normotensive and hypertensive subjects.

However, we[5] have shown that the renal effects of high spinal anesthesia in patients suffering from essential hypertension are variable. In many, renal blood flow is increased and in most, glomerular filtration is depressed. The net renal change is expressive of renal vasodilation during the hypotension caused by spinal anesthesia. In other patients, there is either scant vasodilation or there appear varying degrees of renal ischemia.

We tentatively suggested that the response of the renal vasculature to high spinal anesthesia might be an index of the nature of the hypertensive process. Renal vasodilation after spinal anesthesia might then be taken as evidence of pre-existing increased vasomotor tone, and a failure of such vasodilation, as evidence of humoral vasoconstriction (as from activity of the renal pressor system) or of vascular rigidity due to renal arteriosclerosis. We went on to suggest that where the renal response indicated a predominance of vasomotor influence, sympathectomy should be helpful; and that where the renal vasoconstriction seemed to be due principally to renal pressor activity or vascular narrowing from sclerosis, sympathectomy would probably be unsuccessful.

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The present report is intended as a definitive presentation of the data concerning this hypothesis and includes observations on the renal functional effects of caudal anesthesia.

The major problems posed in the investigation are (1) the nature of the renal functional changes induced by high spinal and caudal anesthesia in patients with essential hypertension, and (2) the possibility of predicting in advance the results of sympathetic ganglionectomy from an analysis of these changes.

METHODS

1. *Spinal Anesthesia Group.*—These patients were under our observation in the clinic of the Lilly Laboratory for Clinical Research, Indianapolis City Hospital. One patient showed normal levels of arterial pressure; one, mild arterial hypertension (prehypertension); and seventeen, varying grades of essential hypertension, including one instance of the malignant syndrome.

Renal blood flow was estimated from Diodrast clearance and hematocrit index. Glomerular filtration rate was taken as equal to plasma inulin clearance. Hematocrit index, plasma protein content, and brachial arterial pressure were measured. These determinations were made one or two days before and again during spinal anesthesia. The measurements reported as control levels of renal blood flow and glomerular filtration are averages of matching calculations from three periods of urine collection and blood sampling. Urine collections were made by washing the bladder through a catheter with 150 c.c. of saline at ten- to fifteen-minute intervals. Results of such individual periods of urine collection during anesthesia are shown graphically in Fig. 2. The calculation of renal arteriolar resistances were made by the method of Lamport.[2] The values summarized in Tables I and III are averages usually of two or three such periods of collection after induction of anesthesia. The level of arterial pressure taken as the control is the average of three or more observations made during the control measurement of renal clearance, and the levels reported during anesthesia are averages of observations made at five-minute intervals. The arterial pressure recorded in all tables is the average of systolic and diastolic arterial pressures and thus approximates mean arterial pressure.

Ballistocardiograms were done in several patients by the method of Starr and Schroeder.[6] The calculations of cardiac index (cardiac output per minute per square meter of body surface) were made by correcting for variations of aortic size to ideal weight and surface area.

Anesthesia* was induced by intrathecal injection. Single injections were given three patients and fifteen were observed by the technique of continuous spinal anesthesia.

2. *Caudal Anesthesia Group.*—The patients studied† were selected from those under observation in the Research Division of the Cleveland Clinic or those recommended to the Section on Neurosurgery for lumbodorsal sympathectomy by the method of Smithwick.

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*The anesthesia was under the supervision of Dr. Lillian Mueller, anesthesiologist, Indianapolis City Hospital, to whom we are most grateful for this assistance.

†We are indebted to Dr. W. James Gardner, who performed these operations, for the opportunity of studying patients under his care.

TABLE I. EFFECTS OF SPINAL ANESTHESIA

NO.	RBF C.C. PER MIN.		GFR C.C. PER MIN.		FF		R_A		R_E		R		Pm MM. HG		TIME		
	C	SP	C	SP	C	SP	C	SP	C	SP	C	SP	C	SP	LEVEL	MIN.	PERIOD
1	1459	1796	145	135	0.20	0.15	0.049	0.017	0.013	0.009	0.062	0.026	147	103	D6	15	1
2	1101	1070	118	95	0.19	0.15	0.055	0.021	0.016	0.014	0.071	0.035	132	93	D6	20	1–2
3	814	1049	120	109	0.23	0.16	0.059	0.034	0.031	0.018	0.090	0.052	135	115	D6	15	1
4	518	746	79	63	0.29	0.13	0.22	0.061	0.053	0.025	0.273	0.086	200	125	D6	12	3
5	1012	1241	96.5	107	0.18	0.17	0.061	0.0099	0.02	0.015	0.081	0.0247	140	90	D6	20	3–4
6	786	1280	82	96	0.18	0.13	0.079	0.016	0.022	0.011	0.101	0.027	133	87	L2	20	1–2
7	1143	1028	97	92	0.18	0.19	0.055	0.014	0.016	0.018	0.071	0.032	138	89	D6	12	5
8	691	975	76	73	0.19	0.13	0.13	0.037	0.027	0.015	0.157	0.052	170	106	D6	30	1–2–3
9	823	906	94	58	0.21	0.13	0.105	0.036	0.013	0.0056	0.118	0.0416	157	97	D5	30	1–2–3
10	581	772	80	44.7	0.26	0.10	0.083	0.027	0.048	0.023	0.131	0.050	138	96	D6	30	1–2–3
11	646	640	97.5	80.2	0.25	0.20	0.095	0.072	0.033	0.027	0.128	0.099	140	120	L1	20	1–2
12	952	1140	145	108	0.25	0.165	0.071	0.044	0.025	0.014	0.090	0.058	140	120	D7	32	1–2–3
13	801	854	103	127	0.24	0.25	0.077	0.055	0.024	0.024	0.101	0.079	138	122	D6	17	3–4
14	408	455	62	62	0.24	0.20	0.148	0.15	0.052	0.04	0.200	0.19	137	147	D9	20	1–2
15	1155	887	80	88	0.14	0.18	0.033	0.048	0.014	0.021	0.047	0.069	110	111	D9	40	1–2–3
16	882	1100	91	91	0.20	0.16	0.059	0.063	0.027	0.018	0.086	0.081	140	150	L2	30	1–2–3
17	618	607	71	83	0.19	0.22	0.062	0.044	0.026	0.03	0.088	0.074	108	95	D6	30	1–2–3

Control (*c*) and observations during anesthesia (*sp*). *RBF* = minimal renal blood flow calculated from plasma Diodrast clearance and hematocrit index. *GFR* = glomerular filtration rate from plasma inulin clearance. Both values are expressed as cubic centimeters per 1.73 square meters of body surface per minute. *FF* = filtration fraction. R_A = afferent resistance; R_E = efferent resistance. $R = R_A + R_E$, all calculated by the method of Lamport. *Pm* = average arterial pressure (mean of brachial systolic and diastolic pressures). *Level* indicates level of anesthesia as estimated from sensory loss. *Time* indicates the duration of the observations under anesthesia listed in the table, and *Period*, the number and approximate timing of the observations under anesthesia. Each period of urine collection extends over 10 to 20 minutes.

The order of the observations in this series was similar to that employed in the former group. It differed in that the clearance of para-aminohippurate was substituted for that of Diodrast in control observations. The analyses were done using a Coleman Model 6 Clinical Spectrophotometer.*

RESULTS

1. *Spinal Anesthesia Group.*—Data obtained from studies in the seventeen patients with essential hypertension are summarized in Table I. Observations on the one patient with minimal hypertension (prehypertension) are recorded in Fig. 2.

Effect on Blood Pressure of Anesthesia Level: Anesthesia reached the nipple line (D 5 to 6) in eleven, D 7 in one, D 9 in two, L 1 in one and L 2 in two patients. Arterial pressure was slightly increased in three patients with anesthetic levels of D 9 and L 2. Pressure was decreased by less than 20 mm. Hg in two patients with sensory loss at D 6, and by more than 20 mm. Hg to a range of from 85 to 125 mm. Hg in twelve whose levels of anesthesia reached from L 2 to D 5. Pressure was transiently decreased below 85 mm. Hg in two patients (Cases 7, 17 A) at sensory anesthetic levels of D 4 and D 5.

Effect on Renal Function: The course of renal function during anesthesia varied with the changes of arterial pressure encountered. No significant change of renal blood flow, glomerular filtration rate, or calculated renal arteriolar resistance occurred in patients whose arterial pressure was not altered or was slightly increased during anesthesia (Cases 14, 15, 16). Decreases of pressure of less than 20 mm. Hg did not alter renal blood flow or glomerular filtration rate in a consistant manner, but resulted in decreased afferent arteriolar resistance (Table I, Cases 13, 17). The effects of decreases of pressure of 20 mm. Hg or more to a range of from 85 to 125 mm. Hg are presented in Table I (Cases 1 through 12) and summarized in Table II. The most frequent changes were increased renal blood flow, decreased glomerular filtration rate and filtration fraction, and decreased resistance of both afferent and efferent arterioles, as illustrated in Fig. 1. The pattern of response is exemplified in Fig. 2, Case 9. The mean average arterial pressure in this group during anesthesia was 103 mm. Hg and the mean decrease of pressure, 43 mm. of mercury.

These relationships of flow, filtration, and pressure are shown in detail for individual periods of urine collection for two patients whose arterial pressure decreased below 85 mm. of mercury. The one (Fig. 2, Case 17 A) showed an initial fall of pressure to 75 mm. Hg, with a decrease of about 30 per cent in renal blood flow and of more than 50 per cent in glomerular filtration rate. A further decrease of pressure to 68 mm. Hg exaggerated these changes. A transient increase of pressure to 100 mm. Hg increased glomerular filtration rate and caused a large gain beyond control levels in Diodrast clearance. As in other circum-

*We are indebted to Dr. Karl Beyer, Sharp & Dohme, Inc., for generous supplies of sodium p-aminohippurate and to Mr. E. D. Coleman, Coleman Instrument Co., for assistance in obtaining the use of a Model 6 Spectrophotometer.

TABLE II. CHANGES IN RENAL FUNCTIONS INDUCED BY SPINAL ANESTHESIA

NO.	RBF	GFR	FF	R_A	R_E	R	Δ PM MM. HG	PM SP. ANESTHESIA MM. HG
1	1.23	1.07	0.75	0.35	0.66	0.42	−44	103
2	0.97	0.81	0.79	0.39	0.91	0.50	−29	93
3	1.28	0.91	0.70	0.58	0.58	0.58	−20	115
4	1.44	0.80	0.45	0.30	0.47	0.34	−75	125
5	1.23	1.11	0.94	0.16	0.73	0.32	−50	90
6	1.63	1.17	0.72	0.20	0.50	0.27	−46	87
7	0.90	0.95	1.06	0.25	1.11	0.57	−49	89
8	1.41	0.96	0.68	0.27	0.57	0.32	−64	106
9	1.10	0.62	0.60	0.35	0.43	0.36	−60	97
10	1.33	0.56	0.38	0.32	0.42	0.36	−42	96
11	0.99	0.83	0.86	0.76	0.84	0.79	−20	120
12	1.19	0.74	0.67	0.61	0.33	0.56	−20	120
Mean	1.225	0.88	0.72	0.38	0.63	0.45	−43	103.4

The values of *RBF*, *GFR*, R_A, R_E, and *R* are the ratios of the observations during anesthesia to observations in control periods. The abbreviations have the same significance as in Table I. ΔPm is the difference between average arterial pressure during control periods and pressure during anesthesia.

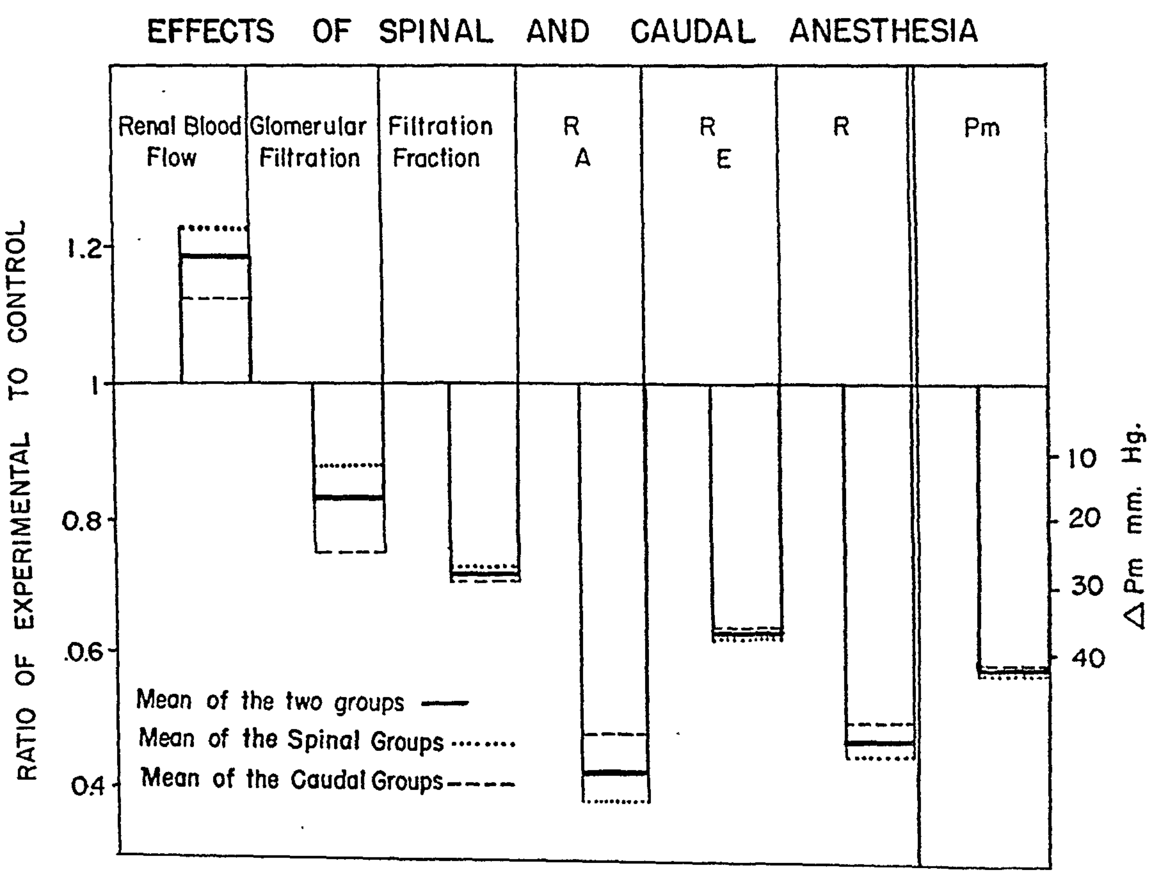

Fig. 1.—The changes in renal function consequent on spinal and caudal anesthesia and means of the changes during the two types of anesthesia. The values indicated are means from Tables II and IV. Changes in renal function are indicated as ratios of experimental observations to those during control. Mean changes in arterial pressure are indicated in mm. Hg from the mean control level.

stances in which hypotension causes partial cessation of glomerular filtration, this "overshoot" of Diodrast clearance is due to washing out, from the tubules, Diodrast secreted but not excreted during hypotension.[7] It is not, as it might seem, a compensatory hyperemia.

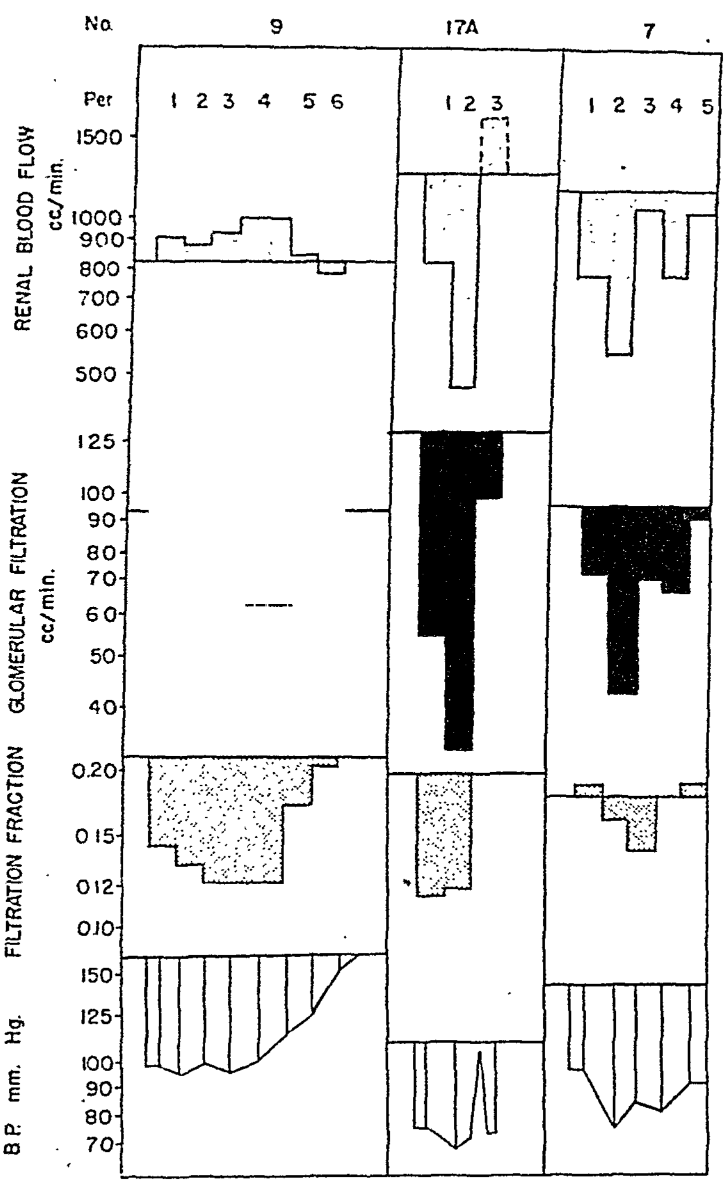

Fig. 2.—Changes in renal function induced by spinal anesthesia in three patients. *No.* = patient number. *Per.* = period of clearance determination under anesthesia, time being approximately ten minutes. The base line for each observation is the mean of control observations. *B.P.* = average arterial pressure in mm. of mercury. Observations on Case 9 are representative of the changes in the group of patients listed in Table II. Changes in Cases 17A and 7 are discussed in the text.

In the other patient (Fig. 2, Case 7), arterial pressure immediately after induction of spinal anesthesia was 95 mm. Hg average. In spite of this apparently satisfactory level of pressure, renal blood flow and glomerular filtration rate were decreased by about 30 per cent. A fall of pressure to 73 mm. Hg exaggerated these changes, but a subsequent rise of pressure to only 82 mm. Hg restored renal function to the levels which had obtained at 95 mm. of mercury. Flow and filtration again decreased when pressure fell to 78 mm. of mercury. Recovery of arterial

TABLE III. EFFECTS OF CAUDAL ANESTHESIA

NO.	RBF		GFR		FF		R_A		R_E		R		Pm		LEVEL	TIME (MIN.)	RESULT OF OPERATION	PERIOD
	C	CA	C	CA	C	CA	C	CA	C	CA	C	CA	C	CA				
18	1208	1012	141	53.5	0.22	0.10	0.0663	0.0422	0.0058	0.0020	0.072	0.046	139	96	D6	32	0	2
19	835	1050	146	93	0.31	0.15	0.057	0.029	0.024	0.0080	0.081	0.037	125	93	D6	25	0	2
20	1230	1228	86.6	100	0.15	0.13	0.052	0.035	0.004	0.005	0.056	0.039	125	105	D8	28	0	3
21	956	943	97.3	37	0.18	0.07	0.200	0.038	0.011	0.004	0.211	0.042	175	96	D5R	15	+	4
22	833	1174	97.4	108	0.21	0.16	0.066	0.029	0.018	0.009	0.084	0.038	132	105	D6	32	+	3
23	595	938	103	89	0.31	0.17	0.098	0.053	0.032	0.007	0.130	0.060	135	109	D5	36		3
24	829	835	78	113	0.15	0.22	0.086	0.049	0.013	0.020	0.099	0.069	141	118	D9	40	0	3
25	976	946	88.4	52	0.16	0.10	0.118	0.034	0.007	0.004	0.125	0.038	178	92	D6	24	+	3
26	796	980	152	183	0.32	0.25	0.117	0.074	0.025	0.014	0.142	0.088	169	140	L1	17	0	1
27	594	807	83	82	0.25	0.18	0.160	0.098	0.016	0.0074	0.176	0.105	155	135	L1	19	0	2
28	704	742	81	98	0.22	0.25	0.147	0.078	0.026	0.031	0.173	0.109	190	150	D9	34		2
29	767	793	79	82	0.20	0.20	0.156	0.100	0.019	0.018	0.175	0.118	200	160	D8	35	0	3
30	1121	799	106	102	0.17	0.23	0.054	0.054	0.010	0.023	0.014	0.077	135	126	L2	38		3
31	909	1004	111	101	0.22	0.19	0.134	0.089	0.015	0.011	0.149	0.100	198	153	L2	34		3
32	638	497	86	65	0.28	0.27	0.182	0.169	0.016	0.02	0.198	0.189	182	149	L3	41	+	3
33	528	754	90	85	0.27	0.18	0.172	0.113	0.026	0.011	0.198	0.124	155	143	D7	13	+	1
34	953	443	80	34	0.17	0.13	0.129	0.182	0.007	0.012	0.136	0.194	180	129	D6	32	0	3
35	834	385	118	29	0.22	0.12	0.1032	0.085	0.012	0.015	0.1156	0.099	145	82	D4		0	

The abbreviations have the same significance as in Table I. Observations under caudal anesthesia are indicated as *CA*. The control observations of *RBF* were made from the plasma clearance of p-aminohippurate and the hematocrit index.

pressure to 88 mm. Hg all but restored these functions to the control levels. Similar initial decrease of blood flow and glomerular filtration at levels of arterial pressure greater than 85 mm. Hg were observed in two other patients (Cases 4 and 5) and were also followed by restoration of these functions to or above control rates at levels of pressure lower than those associated with renal ischemia at the onset of anesthesia.

2. *Caudal Anesthesia Group.*—The eighteen patients studied in this series include one with very mild essential hypertension. The average severity of the disease in this group was greater than in that studied under spinal anesthesia. Most of these patients underwent bilateral lumbodorsal sympathectomy and ganglionectomy. Observations on these patients are listed in Table III.

Effect on Blood Pressure; Level of Anesthesia: Arterial pressure was decreased by less than 20 mm. Hg in two patients whose sensory levels of anesthesia were L 2 and D 7 (Cases 30 and 33). Decreases of 20 mm. Hg or more, but to average levels greater than 125 mm. Hg, occurred in five patients at sensoryanesthetic levels of D 6, D 8, D 9, L 1, L 2, and L 3. In eight patients the drop of arterial pressure was of 20 mm. Hg or more and the levels reached ranged between 85 and 125 mm. Hg (Cases 18 through 25). Sensory anesthetic levels in this group ranged from D 5 to D 9. In one patient (Case 35) the average pressure was less than 85 mm. Hg at a sensory level of D 4.

Effect on Renal Function: No definite changes of renal function were observed in the two patients whose pressure decreased less than 20 mm. of mercury. In the group whose pressures fell by 20 mm. Hg or more to levels greater than 125 mm. Hg, three showed an increase of renal blood flow; two, no change; and one, a definite renal ischemia. Glomerular filtration was increased in two, unchanged in two, and decreased in two subjects. The decrease in glomerular filtration occurring in the patient who showed renal ischemia during the drop in pressure was of the order of 40 per cent.

As in the former series, we are most concerned with the changes of function encountered in patients whose pressures fell by 20 mm. Hg or more to levels of between 85 and 125 mm. Hg average arterial pressure. Comparative preanesthetic and postanesthetic data from these are summarized in Table IV. The averages of

TABLE IV. CHANGES IN FUNCTIONS INDUCED BY CAUDAL ANESTHESIA

NO.	RBF	GFR	FF	R_A	R_E	R	Δ Pm MM. HG	Pm CAUDAL
18	0.84	0.38	0.43	0.64	0.34	0.64	−43	96
19	1.25	0.66	0.48	0.51	0.33	0.45	−32	93
20	1.00	1.15	1.15	0.67	1.26	0.71	−20	105
21	0.98	0.38	0.39	0.19	0.36	0.20	−79	96
22	1.41	0.83	0.76	0.44	0.49	0.45	−27	105
23	1.58	1.10	0.55	0.54	0.22	0.46	−26	109
24	1.01	0.92	1.43	0.57	1.54	0.70	−23	111
25	0.97	0.59	0.63	0.29	0.57	0.30	−86	92
Mean	1.13	0.75	0.73	0.48	0.64	0.50	−42	100

The abbreviations have the same significance as in Table II.

the changes in the group are increased renal blood flow and decreased glomerular filtration. The comparative means of the responses are graphically presented in Fig. 1 where the data from caudal and spinal anesthetic groups are compared and averaged.

With caudal anesthesia, as with spinal anesthesia, decrease of arterial pressure to levels less than 85 mm. Hg resulted in renal ischemia (Case 35). One patient (Case 21) showed renal ischemia and oliguria at pressures of 87 and 81 mm. Hg, which were followed by a return to normal function at 96 mm. of mercury. Two patients (Cases 32 and 34) showed renal ischemia and decreased glomerular filtration at levels of pressure greater than 125 mm. of mercury.

3. *Effect of Spinal Anesthesia on Peripheral Resistance.*—The effects of spinal anesthesia on blood pressure, pulse rate, cardiac output, and peripheral resistance are summarized in Table V. Pulse rate was decreased during anesthesia.

TABLE V. EFFECT OF SPINAL ANESTHESIA ON BLOOD PRESSURE, PULSE RATE, AND CARDIAC OUTPUT

NO.	PERIOD	Pm MM. HG	PULSE (PER MIN.)	CARDIAC INDEX L. PER MIN. PER SQ. M.	P.R. (PER CENT)
5	Control	140	76	2 15	100
	1	115	66	1 74	101
	2	90	66	1 79	76
	3	83	60	1 80	70
8	Control	157	72	1 46	100
	1	125	66	1 2	96
	2	110	60	1.2	85
	3	100	62	1.2	77
36	Control	107	70	1 86	100
	1	75	80	2 13	61
	2	68	60	1 76	67
	3	73	60	1.94	65
13	Control	138	96	1.6	100
	1	135	92	1.7	100
	2	125	84	1 94	81
	3	121	72	1.71	89
	4	117	78	2 00	74
	5	106	78	1.8	74
14	Control	171	69	1.79	100
	1	145	60	1.98	76
	2	147	60	1 96	79
	3	145	60	1 97	76
	4	147	60	1.97	78
15	Control	107	70	1.86	100
	1	75	80	2.13	61
	2	68	60	1.76	66
	3	73	60	1.94	65

No. indicates the number given the patient. *Pm* has the same significance as in other tables. *C.I.* indicates the cardiac index (cardiac output per square meter of body surface) as estimated from the ballistocardiogram. *P.R.* indicates peripheral resistance, calculated from cardiac index and average arterial pressure. The level found in control periods is taken as 100 and levels in succeeding observations under spinal anesthesia are expressed as per cent of the control.

The decrease of arterial pressure after induction of anesthesia was initially associated with decreased cardiac output in three patients. But in later periods of observation in these, and from the outset in the others, peripheral resistance was decreased during anesthesia.

4. *Prediction of Effect of Sympathectomy.*—The evaluation of results of lumbodorsal sympathectomy and ganglionectomy is made in the manner described in the preceding paper.[8] The data are presented in Table III. There is no positive correlation of renal functional changes under caudal anesthesia with the end result of operation. The prediction from renal changes may aid in excluding patients, since results of operation were unsatisfactory in two patients who showed decreased renal blood flow during anesthesia.

DISCUSSION

The effects of spinal and caudal anesthesia are similar. Hence, they are discussed together.

Anesthetic Level and Arterial Pressure.—The degree of change in arterial pressure during anesthesia is not directly related to the level of sensory anesthesia. However, lower levels of sensory loss are usually associated with lesser falls of pressure, and the highest levels of anesthesia (D 4 and 5) are associated with the lowest levels of pressure.

Renal Function.—In every instance in which anesthesia decreased arterial pressure, it induced renal vasodilation, as shown by a decrease in renal resistance (R). The net effect of anesthesia on renal blood flow and function depends on the balance struck between the change in pressure and the change in resistance.

The results in patients whose arterial pressures were significantly decreased (20 mm. Hg or more) to levels ranging about the normal (85 to 125 mm. Hg average pressure) are of special clinical and physiologic interest. These are the levels of arterial pressure reached after successful surgical treatment of hypertension. Further, they represent an abrupt transition from the hypertensive to the normotensive state. The means in this group reveal increased renal blood flow, decreased glomerular filtration rate, and decreased resistance to the flow of blood through the renal arterioles (Tables II and IV). The fact that renal blood flow increases in this group by about 20 per cent during a reduction of arterial pressure which averages 43 mm. Hg is evidence of a positive balance between pressure and resistance. From this it follows that resistance has decreased more than arterial pressure.

Glomerular filtration depends upon the maintenance of a relatively high intraglomerular hydrostatic pressure. It is, therefore, not surprising that glomerular filtration rate is somewhat decreased during the fall in pressure in this group of patients. In normal subjects, glomerular filtration rate is decreased by about 10 per cent during spinal anesthesia which reduces arterial pressure to 89 mm. of mercury.[1] In our patients it is reduced about 17 per cent during a drop in pressure to 103 mm. of mercury. The depression of filtration rate in the hypertensive group

is by no means great enough to jeopardize renal excretory function. However, the decrease in filtration appears in these patients at a mean average arterial pressure of 103 mm. Hg rather than 89 mm. Hg, and averages 17 rather than 10 per cent. This suggests that in the hypertensive patient there is some factor which prevents all the normal gradient of arterial pressure from reaching the glomerular capillaries. The most probable factor is a residual increased afferent arteriolar resistance, not abolished by spinal or caudal anesthesia. The decreases in afferent and efferent arteriolar resistances which occur during anesthesia indicate that anesthesia results in vasodilation consequent on denervation. The abnormal residue of afferent resistance which tends to interfere with glomerular filtration under anesthesia in hypertensive patients may be construed as a vasoconstriction of humoral origin such as might result from the activity of the renal pressor system or as an inability of the afferent arterioles to dilate consequent to arteriolosclerosis.

The significant conclusions from the data obtained in this group of patients are that there is no essential qualitative abnormality in the renal vascular responses of hypertensive patients to spinal or caudal anesthesia, and that the changes which do appear are principally the result of renal vasodilation.

Our data would seem at first glance to contradict those of Gregory and coworkers,[4] who observed decreased rather than increased renal blood flow during hypotension due to spinal anesthesia in hypertensive patients. The contradiction is largely due to the choice of different experimental methods. These observers carried the level of anesthesia to D 2 or higher, thus obtaining lower levels of arterial pressure during anesthesia than prevailed in most of our observations. Intervals of collection extended over one hour in their experiments, whereas in ours the changes in renal circulation were measured at frequent intervals. However, we are unable to explain their failure to observe a rather consistent decrease of filtration fraction during hypotension.

Certain of our observations agree very well with those of these workers. Thus, at levels of average pressure less than 85 mm. Hg, we found depression of renal blood flow and glomerular filtration. Similar changes appear during hypotension in normal subjects.[1] Their presence is not evidence of a specific hypertensive abnormality. Our data also agree in that two patients showed decreased renal blood flow and filtration rate at pressure levels greater than 125 mm. of mercury. The cause of the failure of renal vasodilation in these patients is not apparent. It may be that the effect of anesthesia was inadequate or that the renal arterioles in these patients were so diseased as to be incapable of vasodilation. The tendency in certain patients for blood flow and glomerular filtration to decrease during the drop of pressure immediately after induction of anesthesia and then to return to control levels or above as anesthesia and hypotension continue is of particular interest. As we have seen, most hypertensive patients respond to anesthesia and hypotension by renal vasodilation, from which it may be concluded that the normal capacity of the renal vessels to adapt to changing levels of arterial pressure is maintained. In two patients this capacity seemed to be lost. It seemed to be slowed in the patients showing a biphasic response of blood flow resistance and blood pressure. The biphasic pattern of change in renal resistance

was paralleled in three patients by the changes of peripheral vascular resistance (Table V). This was unchanged immediately after anesthesia and later fell as hypotension persisted. The mechanism of this adaptative sequence is a matter of speculation.

In summary, spinal and caudal anesthesia induce, in most patients with hypertension, decrease in arterial pressure, increase in renal blood flow, and a slight decrease in glomerular filtration. The sequence of these renal changes is only consistent with renal arteriolar vasodilation. In a few patients this renal response is deficient or slowed.

Mechanism of Vascular Responses.—The cause of the changes in renal and systemic vascular resistance must now be examined. Does the decrease in resistance result from decreased cardiac output and arterial pressure, or as seems more likely, does the decrease of pressure result from decreased peripheral resistance, in which renal resistance is a large component? Smith and co-workers[1] suggested that the hemodynamic changes caused by spinal anesthesia in normal subjects reflect decreased venous return, with consequent decreased stroke volume and cardiac output and a resultant decrease of arterial pressure. They attributed the decrease in venous return to postarteriolar (capillaries, venules, veins) dilatation due to widespread paralysis of skeletal muscle. Widespread muscle paralysis does not occur in the course of caudal anesthesia. The renal and systemic vascular responses to spinal and caudal anesthesia are very similar, if not identical. We must conclude, therefore, that postarteriolar dilatation with decreased venous return due to muscle paralysis is not the principal factor in the hemodynamic changes induced by either spinal or caudal anesthesia.

This conclusion is confirmed by our observations on the effect of spinal anesthesia on cardiac output and peripheral resistance. Three patients showed decreased output and arterial pressure with unchanged peripheral resistance at the outset of anesthesia. This sequence is consistent with decreased venous return and cardiac output as the major factor in lowering blood pressure. Later in these observations, however, and throughout the others, the principal element in the decrease of arterial pressure is decreased peripheral resistance. To the extent that cardiac output remains slightly depressed in some of these observations, it may be that venous return is slowed by skeletal muscle paralysis. But the large decreases in both peripheral and renal resistances speak for actual arterial and arteriolar dilatation. Unfortunately, no data on cardiac output are available for the caudal anesthesia group. If our view is correct, caudal anesthesia should differ from spinal anesthesia in that the decrease of arterial pressure would be entirely, rather than only principally, due to decreased peripheral resistance.

Thus, the mechanism of the renal and systemic vascular changes accompanying spinal and caudal anesthesia seems to be principally arteriolar vasodilation, although venous pooling with decreased venous return may contribute to the tendency to decreased cardiac output in patients submitted to spinal anesthesia.

Vasodilation is thus seen to be a major factor in the decrease of arterial pressure, and since it is elicited by a procedure which temporarily paralyzes spinal outflow, it must be concluded that it is due to interruption of nerve im-

pulses. In normal subjects, such vasodilation results only in maintenance of normal rates of renal blood flow at slightly decreased arterial pressures, and reflects the autonomy of the renal circulation, that is, the capacity to maintain normal rates of blood flow during wide fluctuation of pressure. In hypertensive subjects the vasodilation is commonly followed by an actual increase in renal blood flow in the face of considerable decreases of arterial pressure. We must conclude that the renal vessels of hypertensive patients are under abnormal stimulation to an extent that denervation often results in vasodilation and increased renal blood flow at approximately normal levels of arterial pressure. So large a fraction of the cardiac output traverses the renal circulation that a considerable proportion of the decrease in peripheral resistance observed in some hypertensive patients is contributed by renal vasodilation. But we confirm the view of Gregory and Levin[9] that increased renal blood flow is not the cause of the decrease in arterial pressure during high spinal anesthesia.

The mechanism by which high spinal and caudal anesthesia lead to vasodilation of arterioles, including those of the kidney, is unknown. Our unpublished observations on the effect of these procedures in dogs with experimental renal hypertension due to perinephritis show an exact similarity with the renal functional changes found in hypertensive patients. These procedures do not, therefore, reveal a difference in mechanism between experimental hypertension of known renal origin and the essential hypertension of human patients, as we had once thought they might. Both types of anesthesia cause a functional denervation which we assumed to be equivalent to that of lumbodorsal sympathectomy with ganglionectomy. But this operation does not increase renal blood flow in hypertensive patients, nor does it decrease arterial pressure in renal hypertensive dogs. It is possible that the vasodilation caused by high spinal and caudal anesthesia is due to a denervation other than that which is effected by lumbodorsal sympathectomy and ganglionectomy, or that the differences between the responses to operation and to anesthesia reflect the difference in the duration of the two procedures. Again, it may represent a change in the vasoconstrictor-vasodilator balance of vascular responsiveness of the order similar to that observed after injection of tetraethyl ammonium or destruction of the spinal cord.[10]

Our observations are entirely inconsistent with the view that essential hypertension is a compensation for increased renal vascular resistance, whether due to arteriosclerosis or other causes. True, a decrease of arterial pressure to very low levels depresses renal blood flow in hypertensive patients. But the same is true in normal subjects. In a few patients renal blood flow falls below control levels at levels of arterial pressure which are normal or above the normal, and it may be that in these the disease has advanced to the point where the vessels can no longer adjust to normal levels of arterial pressure. These instances, however, are exceptional in this group. The slight decrease in glomerular filtration which may occur during spinal and caudal anesthesia, even in subjects whose renal blood flow has been increased, suggests a presence of a small degree of fixed abnormal afferent arteriolar resistance. Clinically, this residue is insignificant and cannot serve as a contraindication to procedures which decrease arterial pressure.

Prediction of Effect of Sympathectomy.—Our hope of predicting the end result of lumbodorsal sympathectomy and ganglionectomy was not realized. This fact supports the view that the hemodynamic effects of sympathectomy differ significantly from those occurring during spinal or caudal anesthesia.

CONCLUSIONS

1. High spinal or caudal anesthesia which reduces average arterial pressure in hypertensive patients by 20 mm. Hg to levels ranging from 85 to 125 mm. Hg usually causes renal vasodilation, resulting in increased renal blood flow and a slight decrease in glomerular filtration rate. The observations are inconsistent with the view that essential hypertension is a compensation for increased renal vascular resistance.
2. Qualitatively, the renal vascular responses of normotensive and hypertensive patients to these procedures are identical. Quantitatively, they may differ slightly in that, in hypertension, a fraction of afferent arteriolar resistance is not removed by anesthesia.
3. The renal vasodilator response to anesthesia in hypertension indicates that a large proportion o' increased renal vascular resistance in this disease is dependent on nervous influences which are affected by anesthesia extending to about D 5, or that denervation by anesthesia has sensitized vasodilator influences.
4. The major hemodynamic change induced by spinal or caudal anesthesia is seen to be due to decreased peripheral resistance.
5. Exceptionally, a few hypertensive patients show deficient or slowed renal vasodilator responses to spinal or caudal anesthesia. Two such patients failed to benefit from lumbodorsal sympathetic ganglionectomy. But operation was equally ineffective in patients whose responses were vasodilator. The renal vascular response to anesthesia is not a positive guide in the selection of patients, although the absence of vasodilation during anesthesia may contraindicate operation.

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EXPERIMENTAL STUDIES ON AURICULAR FLUTTER AND AURICULAR FIBRILLATION

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IT IS possible to produce an auricular tachycardia of approximately 200 to 300 beats per minute by the injection of 0.05 c.c. of a 0.05 per cent solution of aconitine into the walls of the auricles.[31] In the experiments in which this observation was made the site of the injection was the left or right auricular appendix. The tachycardia appeared within one or two minutes and lasted as long as sixty minutes. Faradic stimulation of the vagus nerves in the neck during the presence of this tachycardia provoked a remarkable acceleration of the rate in all experiments. In some instances this increase in rate exceeded 100 per cent. Isolation of the injected auricular appendix from the rest of the heart by a clamp immediately ended the tachycardia. Upon removal of the clamp the tachycardia reappeared within a few seconds. Cooling of the site of injection immediately abolished the tachycardia. It recurred quickly and invariably whenever the cooling thermode was removed.[31]

In the earlier experiments it could not be decided whether the tachycardia was auricular flutter or whether it was an "essential" paroxysmal tachycardia. In these experiments vagal stimulation never terminated the tachycardia nor was auricular fibrillation or the phenomenon of re-excitation observed to follow this maneuver. Repeated reference has been made to the difficulties encountered in differentiating between auricular flutter and paroxysmal auricular tachycardia, and the possible identity of these conditions has been discussed.[3,5,9]

If a circus movement causes the tachycardia which follows the injection of aconitine, the result of cooling is unusual. One would be forced to assume that the circus wave is always located at the site of the injection in the auricular appendices. While it is conceivable that a circus movement ceases when the path of the circulating wave is cooled, it is difficult to explain how the circus movement always recurs immediately when cooling is interrupted. The increase of rate during vagus stimulation is, according to the circus movement theory, readily explained. The shortening of the refractory phase causes islands of refractory tissue to disappear and makes the central wave move faster on its shortened path.

If it is assumed, however, that the mechanism underlying the tachycardia is a rapid stimulus formation in a center rather than a circus movement, then

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the increase of rate during the vagus stimulation is an unusual phenomenon which requires explanation. The effect of the cooling is readily understandable.

In order to shed more light on the problems involved, experiments were resumed, with one important modification. The aconitine was injected in the area of the head of the sinus node, near the angle between the superior vena cava and the right auricular appendix. In this way, it was hoped that the response of specific tissue to the focal administration of aconitine could be determined.

METHOD

The hearts of dogs were exposed in the usual manner during Nembutal anesthesia. Artificial respiration was instituted. The vagus nerves were cut in the neck. The electrocardiogram was invariably taken on Lead II. The solution of aconitine was prepared in the same concentration that was used in previous experiments (0.05 per cent); since it deteriorates rapidly, no solution older than four weeks was used. As has been stated, 0.05 c.c. of the solution was injected near the head of the sinus node into the taenia terminalis. The presence of additional subepicardial connective tissue and of a greater muscle mass at this site usually prevents direct injection into the blood stream; this accident often precipitates ventricular fibrillation immediately. Only three of twenty-one experiments were marred by the development of ventricular fibrillation soon after the injection.

RESULTS

Auricular Fibrillation and Cooling of the Focus of Injection.—The injection of the aconitine solution around the sinus node was invariably followed by the sudden onset of a regular tachycardia with the same average rate and other characteristics that were observed in the tachycardia resulting from injection into the appendices.[21] The P waves were always high and positive in Lead II and the rate was extremely regular. An important difference, however, was the frequent appearance of auricular fibrillation, which was observed in fifteen experiments. In twelve experiments auricular fibrillation appeared spontaneously and three times it was observed during or shortly after faradic stimulation of a vagus nerve. Occasionally, it lasted only a few seconds or minutes, but in nine experiments it persisted for the duration of the experiment unless it was abolished by certain measures which will be discussed presently.

In the first portion of the tracing shown in Fig. 1, there is a regular auricular tachycardia with a rate of 352 per minute. There is a 2:1 A-V block. Faradic stimulation of the right vagus immediately led to auricular fibrillation (middle of the tracing) with an auricular rate of approximately 1,500 impulses per minute. The beginning and end of the brief vagus stimulation are clearly visible because the induction current deforms the tracing slightly.

The change from the regular auricular tachycardia to fibrillation, and vice versa, often occurred independently of vagus stimulation. Thus, in Fig. 2,*A*, a regular auricular tachycardia with a rate of 370 changes into auricular fibrillation shortly after faradic stimulation of the right accelerans nerve; the tracings shown

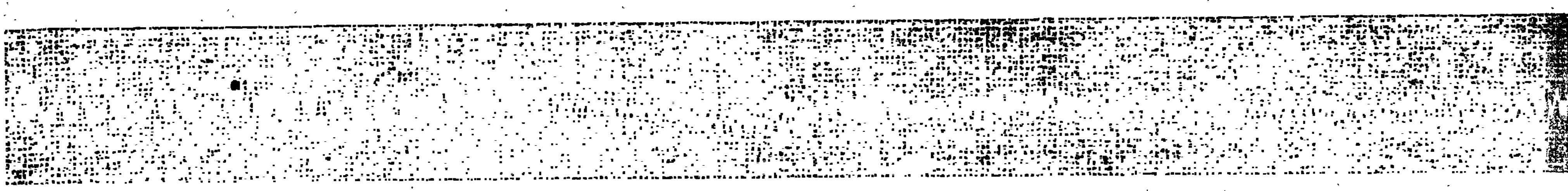

Fig. 1.—Faradic vagus stimulation changes auricular flutter into fibrillation.

A.

B.

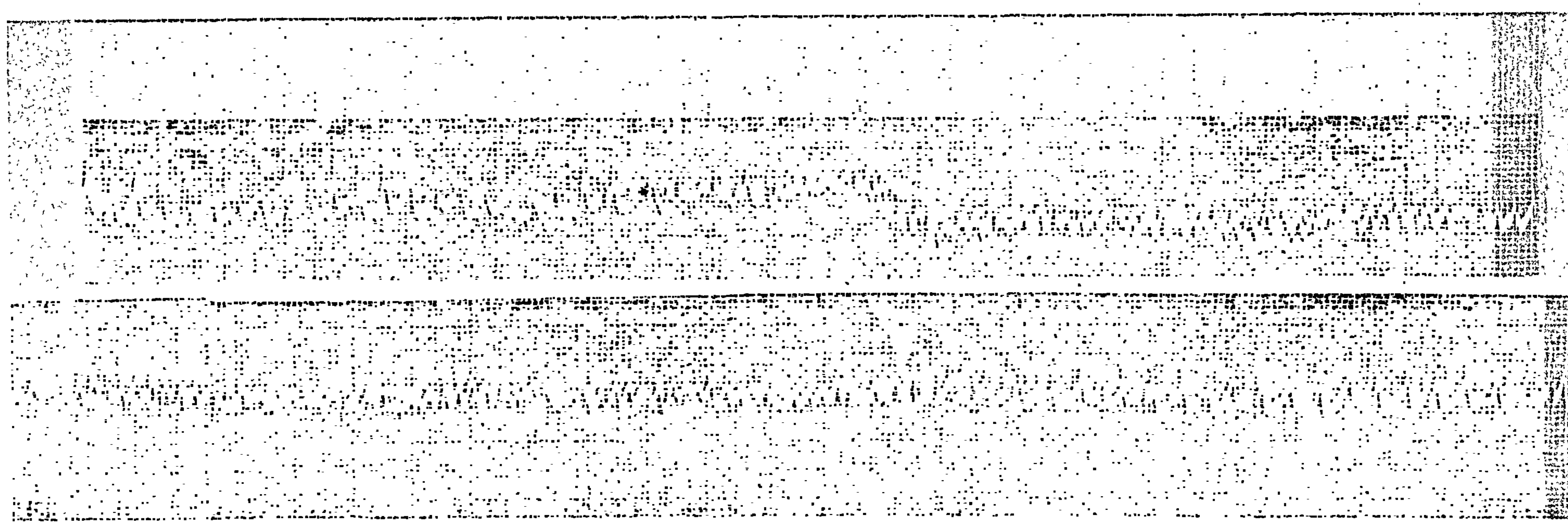

Fig. 2.—*A* shows the change from flutter into fibrillation; in *B*, fibrillation changes into flutter.

in Fig. 2,*B*, were obtained in another experiment, and auricular fibrillation, which had appeared soon after stimulation of the right accelerans nerve, changes into a regular auricular tachycardia with a rate of 300 per minute.

Cooling of the injected area in the region of the head of the sinus node was attempted in those experiments in which fibrillation, either induced by vagus stimulation or arising spontaneously, persisted for any length of time. The site of injection was clearly visible as a small gray blister with a diameter of 2.0 to 3.0 mm.; it was formed by the separation of the epicardium from the underlying tissue. In nine experiments, the cooling with a thermode promptly abolished the auricular fibrillation and led to sinus rhythm. Cessation of the cooling caused the immediate reappearance of the fibrillation. If the cooling was continued for more than two or three seconds, then at the end of the cooling the regular tachycardia appeared first and was soon followed by auricular fibrillation. This effect of cooling was obtained repeatedly (up to four times) during the same experiment.

Fig. 3 shows two tracings which demonstrate the effect of cooling. The top tracing shows auricular fibrillation which appeared after the injection of aconitine and persisted throughout the experiment. Cooling immediately abolished the fibrillation and two normal sinus beats are seen. The second sinus beat is again followed by fibrillation, since the thermode was immediately removed when the fibrillation ceased. The interval between the first abolition of fibrillation and its reappearance in Fig. 3,*A*, is seen to be less than 2.5 seconds. In the second tracing (Fig. 3,*B*), recorded in another experiment, persistent auricular fibrillation also followed the injection of aconitine in the area of the head of the sinus node. In this instance the cooling was applied for a longer time. Cooling immediately produced sinus rhythm. After the cooling, the thermode was removed and a regular tachycardia can be seen to follow. At the sixteenth beat this again changes into fibrillation. The interval between the end of the fibrillation and the reappearance of the tachycardia measures approximately 6.8 seconds. The appearance of a regular auricular tachycardia after the fibrillation had been stopped by cooling and its quick and spontaneous change into auricular fibrillation was repeatedly seen in several experiments.

Only when auricular fibrillation followed the accidental injection of a minute amount of the aconitine into the blood stream, or when the aconitine was spilled over a larger area of the right auricle, or when late in the experiment the aconitine spread by diffusion over the auricular muscle did cooling of the site of injection fail to bring the auricular fibrillation to a sudden end.

In eleven experiments a regular auricular tachycardia followed the injection of aconitine. As will be pointed out, we consider this regular tachycardia to be auricular flutter. Cooling of the injected area invariably and immediately abolished this tachycardia, which returned within one to two seconds after the cooling was interrupted. Table I shows the auricular rates before and after cooling. It is evident from the table that the rate immediately after the return of the tachycardia was, with rare exceptions, the same as the rate before the cooling.

A.

B.

Fig. 3.—In *A*, auricular fibrillation is stopped by cooling the focus of injection of aconitine; removal of the thermode caused the fibrillation to reappear. In *B*, the cooling was continued for a longer time. After interruption of the cooling, flutter appears and is soon followed again by fibrillation.

A.

B.

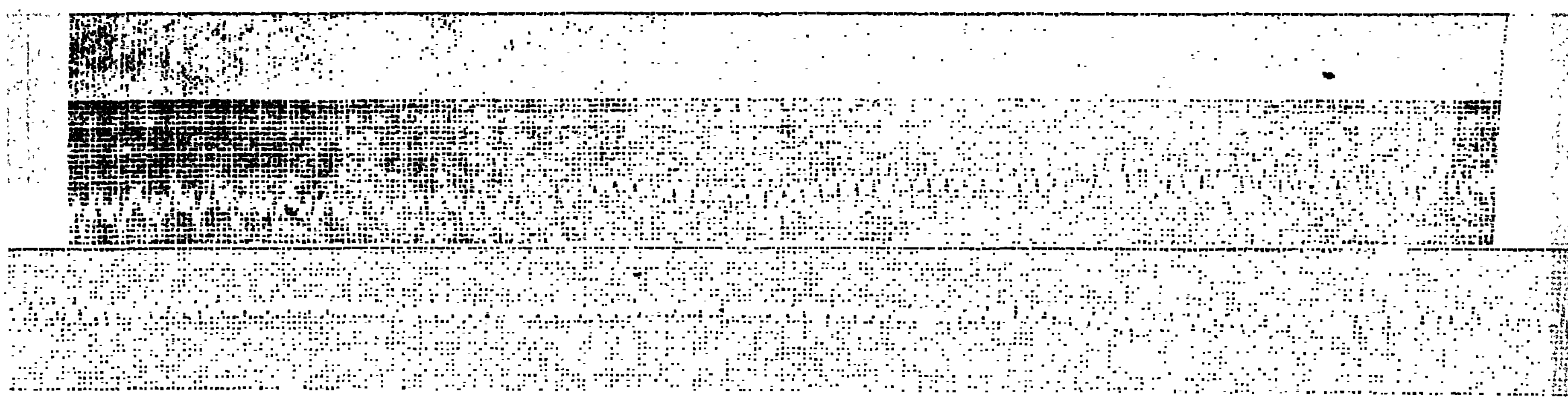

Fig. 4.—*A* shows, at the beginning, auricular flutter with 2:1 A-V block. During vagus stimulation the rate of the auricle increased slightly. In *B* vagus stimulation was accompanied by a considerable increase of auricular rate.

TABLE I. AURICULAR RATE BEFORE AND AFTER COOLING

DATE	BEFORE	AFTER
12/31	330	330
	300	300
1/24	230	230
	248	248
2/4	248	248
	214	214
	272	272
	240	240
2/18	272	272
2/26	352	352
	272	272
3/4	248	230
	230	240
	330	330
	230	230
3/18	214	230
	[illegible]	300
3/25	375	375
4/1	300	300
	426	426
	330	330
4/8	290	272
4/29	390	390

Vagus Stimulation During the Regular Tachycardia.—Whenever the solution of aconitine was injected into the auricular appendices, vagal stimulation caused a remarkable increase of the rate of the auricles.[31] After an injection of aconitine into the region of the head of the sinus node, faradic stimulation of the right or left, or both, vagus nerves failed to increase the rate in three out of thirteen experiments. In most of the other experiments the rate increased only moderately, even when both vagus nerves were stimulated simultaneously. In some instances the rate underwent a considerable increase whenever vagus stimulation was tried. Table II shows the rates of the auricle before, during, and immediately after vagus stimulation in all instances in which it was tried. In all experiments in which vagus stimulation increased the auricular rate, the rapid return of the rate to its former level as soon as the stimulation was discontinued was clearly evident.

In Fig. 4,*A*, (date of experiment indicated in Table II as 1/7), the auricular rate is 428 and the ventricular rate is 214 per minute, with the blocked P waves hidden in the QRS complex. During faradic stimulation of the right vagus nerve in the neck, the 2:1 A-V block disappeared and a complete A-V block developed. The auricular rate increases to approximately 461 per minute. After the vagus stimulation was stopped, the disturbance of the A-V conduction persisted for some time but the picture which existed before the stimulation soon reappeared.

The tracing shown in Fig. 4,*B*, (date of experiment indicated in Table II as 3/18) was obtained in another experiment. A regular auricular tachycardia with a rate of 280 per minute and partial A-V block are seen. Faradic stimulation of the right vagus in the neck again inhibited A-V conduction completely and simul-

taneously increased the auricular rate up to 500 per minute. A slight auricular arrhythmia, with group formation of three auricular beats followed by a longer diastole, is visible. With interruption of the vagus stimulation the initial picture reappeared quickly. This is one of the rare instances in which the form of the P waves changed during vagus stimulation.

TABLE II. AURICULAR RATE BEFORE, DURING, AND AFTER VAGUS STIMULATION

DATE	BEFORE	DURING	AFTER
11/26	300	330	300
	428	461	426
	352	375	352
12/17	214	230	214
	248	262	248
	290	316	290
12/31	248	260	248
1/7	214	230	214
	428	500	428
2/4	248	285	248
	272	300	300
	230	248	187
2/11	374	374	374
	300	330	300
2/18	332	375	332
	352	275	352
3/4	248	290	248
	230	260	230
3/18	230	230	230
	300	361	300
	332	375	332
	280	500	280
3/25	248	260	248
	300	330	300
4/1	285	375	285
	300	461	300
	285	332	285
	332	374	332
4/8	214	214	214
	214	214	214
	214	214	214
4/29	340	375	340

DISCUSSION

The frequent change from the auricular tachycardia into auricular fibrillation, and vice versa, which was observed during vagus stimulation or followed cooling or developed spontaneously, shows, in our opinion, that we are dealing with auricular flutter in these experiments and in those previously reported.[31] The appearance of "rapid re-excitation" was observed by Lewis even when the auricles were driven by artificial stimuli, but in tracings like those shown in Fig. 1 where auricular fibrillation persisted in an unchanged form long after the end of the vagus stimulation, we are dealing with simple auricular fibrillation. Clinically and experimentally the change from flutter to fibrillation and vice versa is a common event, while the change from auricular tachycardia to fibrillation or from fibrillation to a paroxysmal auricular tachycardia is practically

unknown. When an auricular tachycardia with a rate between 200 and 300 occurs after an attack of auricular fibrillation has been stopped by focal cooling, as shown in Fig. 3,*B*, and when this tachycardia changes within a few seconds into auricular fibrillation, we feel justified in calling this auricular tachycardia auricular flutter.

Our inability to stop the auricular tachycardia, even with the strongest faradic stimulation of a vagus nerve, is more readily understood if auricular flutter exists. The arrest of auricular flutter by vagus stimulation is unknown, while it is a common phenomenon in auricular tachycardia. This difference of response is one of the reasons why we are inclined to insist on separating the two conditions in spite of a recent tendency to regard them as identical. The auricular rate in auricular flutter has been found to be increased during vagus stimulation experimentally[22,29] and clinically.[35]

The interruption of the auricular fibrillation by cooling the area into which the injection was given, an area with a diameter of only a few millimeters, might be compatible with the circus movement theory of Lewis. Cooling prolongs the refractory phase[6] and in this way might end the circulation of the central wave. Actually, termination of fibrillation by perfusing the heart with a cool fluid has been observed[14,28] and, in a footnote of his book, Lewis remarked: "Fibrillation, like flutter may also on occasion be terminated by cold and pressure, very locally applied. All such effects presumably depend upon interference with a single circulating wave.[20] With the technique used by Lewis, who studied the short runs of fibrillation which follow faradization of the auricle, the reappearance of auricular fibrillation after its termination by cooling could not be observed. In our experiments the fibrillation invariably recurred as the cooling was stopped. Its reappearance cannot be explained if a circus movement proceeds up or down the taenia terminalis unless we accept the existence of a center for abnormal stimulus formation. If the presence of a center of formation of abnormal stimuli in these tracings is assumed, the conception of a circus movement, in the sense that Lewis used this term, can be abandoned. It might be proposed that forms of circus movement exist, such as, for instance, those suggested by Garrey[13] and Ashman and Hull.[1] It is, however, difficult to imagine how an injection of aconitine anywhere into the auricular wall should invariably lead to the special conditions which, according to these authors, are necessary to cause the appearance of circus waves.

We do not intend to imply, however, that circus movement or the phenomenon of re-entrance does not occur. This is known to exist in muscular rings in the frog heart between auricle and ventricle, in simple muscle strips,[32] and under special conditions even in the mammalian heart.[30,34]

If a circus movement is rejected and if we attribute the auricular flutter in these tracings to a rapid stimulus formation in a center, the increase of rate during vagus stimulation must be explained by a direct stimulating vagal action on the center. Rothberger and Winterberg,[29] who observed the increase of rate in auricular flutter during vagus stimulation, discarded this possibility in view of the well-known inhibitory action of the vagus on the different properties of the heart. These authors thought that the shortening of the refractory period

during vagus stimulation is in some way responsible for the increase of rate, but they gave no clear idea of how this could take place.

It has become clear in recent years that, coinciding with the *inhibitory* effects of the vagus on the contractility of the auricles and on conduction from the sinus node to the auricles and from the auricles to ventricles, other "positive" and, therefore, somewhat paradoxic effects of the vagus on the heart occur. They are, to some extent, encountered regularly and, in part, only under certain circumstances; repeatedly, the presence of accelerator fibers in the vagus has been postulated. Thus, increase of rate upon vagus stimulation was observed in the nicotinized mammalian heart.[4] Since the paradoxic effect appeared after a period of latency which was scarcely noticeable, an action of sympathetic fibers can be ruled out. The vagus does not inhibit conduction from fiber to fiber in auricular muscle.[22,25] If the intra-auricular conduction is impaired by cooling or pressure, vagus stimulation improves it and restores normal conditions.[21] The recovery of auricular tissue after conduction is extremely rapid during vagus stimulation.[8] If a complete block was produced within the auricular tissue by application of a clamp, and this lasted for forty minutes, it was immediately abolished by vagus stimulation.[21] This effect can hardly be explained by the shortening of the refractory phase alone. The excitability of the auricle during vagus stimulation, which for many years was believed to be depressed, was found to be augmented. This has been demonstrated repeatedly by determination of the chronaxie[10,11,17,27] and also by the threshold method.[10]

The finer mechanism of stimulus formation is unknown. Whether we assume a rhythmic formation of stimuli or a rhythmic response to a continuous stimulus, it is clear that the rate depends on the length of the refractory period and that a shortening of this period may increase the rate directly.[2]

Faradic stimulation of the right or left vagus nerve in the neck during auricular flutter elicited by the topical administration of aconitine to the auricular appendices invariably leads to a marked acceleration of rate.[31] In the series of experiments reported in this paper, however, the injection of aconitine into the region of the head of the sinus node and faradic stimulation, even with the secondary coil over the primary coil, failed in three experiments to alter the auricular rate or caused but a moderate increase of rate.

We consider it possible that whenever stimulation of the vagus nerves with the strongest faradic currents did not alter the rate of the flutter, or influenced it only slightly, the focus of stimulus formation was in the specific tissue of the sinus node. A focus in the muscle of the taenia terminalis responded in the same way as foci in the appendices, that is, with marked acceleration. The specific tissue of the sinus node and of the A-V conduction system has a refractory period which is about 30 per cent longer than that of the auricular muscle,[7,19] and its excitability as measured with the chronaxie method is about three times lower.[18] There is experimental evidence to favor the assumption that the refractory period of the specific tissue is less influenced by vagus stimulation than is that of the auricular muscle.[24]

On the basis of the available evidence we believe it is possible that auricular flutter and fibrillation are caused by rapid stimulus formation in one center.

With a rapid rate of stimulus formation, islands of refractory muscle appear, just as conceived by Porter and proved by Lewis and his collaborators. Due to the presence of these islands, local dissociations appear; re-entrant waves and local circus movements are made possible. These are not the cause of fibrillation but a concomitant feature. It is well known that it is impossible to cause auricular fibrillation by faradization of isolated specific tissue.[33] On the other hand, without specific tissue no fibrillation appears.[26] A certain muscle mass is necessary for the development of fibrillation.[12] We, therefore, conclude that specific tissue is necessary for the stimulus formation and that the muscle mass with the blocked areas leads to weaving and interweaving of stimuli traveling over the heart.

SUMMARY

Injection of aconitine into the region of the head of the sinus node causes auricular tachycardia with a rate between 200 and 400 per minute. Often auricular fibrillation appears spontaneously or follows vagus stimulation. The change of the auricular tachycardia into fibrillation and vice versa, which was often registered, shows that the auricular tachycardia is auricular flutter and not "paroxysmal auricular tachycardia."

Cooling of the focus of injection immediately abolishes the fibrillation which reappears when the cooling is interrupted. These results cannot be explained by the circus movement theory of Lewis. They can only be explained by assuming that auricular flutter and fibrillation are initiated by rapid impulse formation in a single center. As the impulses thus formed move into the larger mass of auricular muscle, islands of refractory tissue appear, which cause a weaving and interweaving of the contraction process that is characteristic of fibrillation.

The increase of auricular rate during vagus stimulation in the presence of auricular flutter is caused by a direct action of the vagus on the center of stimulus formation. Shortening of the refractory phase increases the rate of stimulus formation.

When flutter originates in the auricular appendices the increase in rate during vagus stimulation is greater than when it originates in the area of the sinus node. The vagus effect on the refractory phase seems to be less pronounced on specific tissue than on auricular muscle.

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CELLOPHANE TREATMENT OF SYPHILITIC ANEURYSMS WITH REPORT OF RESULTS IN SIX CASES

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ALTHOUGH syphilitic aneurysms of the thoracic aorta may possibly become nonexistent within the next few decades of penicillin therapy, a sufficient number still persist, expand, and rupture to warrant adoption of a practical and relatively simple surgical treatment. The limited applicability, poor results, and numerous fatal complications accompanying the various blind wiring techniques of aneurysms led to their almost complete abandonment over a decade ago.

The distorted anatomy, invasive tendencies, large size, and friable, thin walls of these aneurysms contraindicate any attempt at extensive surgical manipulation in the form of resections or anastomoses. The pounding, pulsating pressure exerted by these aortic dilatations presents an almost malignant tendency to invade and penetrate any adjacent soft tissue. Ordinary soft tissues offer little resistence, and even the ribs and sternum can be eroded by an expanding, pulsating aneurysm.

The intense foreign body reaction produced by cellophane with its constricting fibrosis seemed to offer the simplest and most satisfactory method of at least curbing the expansion, and possibly constricting these aneurysmal dilatations. This possibility was suggested by the report of Harrison and Chandy[1] who had gradually eliminated two arteriovenous aneurysms of the subclavian vessels by cellophane. Harrison's clinical application of the material was in turn suggested by Pearse,[2] who had demonstrated the ability of cellophane as an improved method of gradual obliteration of the lumen of important blood vessels, such as the internal carotid, in the place of the previously devised and somewhat unsatisfactory clamps and bands. This constricting property of cellophane had been demonstrated originally by Page,[3] who used it in 1939 to produce artificial nephritis and hypertension in dogs by wrapping it around the kidneys.

A dilemma arose, however, from the reports of McKeever[4] and others that cellophane produced no reaction and was suitable for reconstructing tendon sheaths and lining joint spaces. An experimental study was undertaken at Washington University School of Medicine with several representative chemically different varieties of cellophane, supplied through the courtesy of the DuPont de Nemours Company of Wilmington, Del. The results of this in-

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vestigation, published in greater detail elsewhere,[5] suggested that a new type known as Polythene cellophane produced the most intense fibrotic foreign body reaction, whereas some of the other types produced little if any reaction.*

Polythene cellophane was selected, therefore, to wrap syphilitic aneurysms of the thoracic aorta to induce an intense, foreign-body fibrous tissue reaction around the aneurysm, thereby preventing its further expansion and eventual rupture. It was hoped also that the constrictive action of the scar tissue might even reduce the already existing dilatation of the lumen of the aneurysm.

OPERATIVE TECHNIQUE EMPLOYED

Under endotracheal anesthesia the patient is placed on the side opposite the aneurysmal dilatation of the thoracic aorta. Through a paravertebral incision extending around the angle of the scapula, the entire length of the fifth or sixth rib is resected and the pleura opened through the bed of the resected rib. The lung is retracted and the mediastinal pleura dissected free from the aneurysm, exposing as much of the surface of diseased aorta as can be safely freed without danger of rupture. It is frequently impossible to free the entire circumference of the descending aorta because of beginning erosion of the vertebrae and ribs around the origins of the intercostal vessels. The pleura may also be too attenuated and adherent over thin bulging areas to permit its complete removal. A sheet of Polythene cellophane is then cut to fit the dilated portion of aorta without extending over adjacent normal structures. This cellophane is sutured loosely to any suitable mediastinal tissue with fine silk sutures, care being taken not to pass any sutures directly into the wall of the aneurysm.

SUMMARY OF RESULTS

Polythene cellophane was used to wrap the six syphilitic aneurysms of the thoracic aorta reported in Table I.

The last two patients included in the table were treated too recently to permit any definite evaluation of their symptoms, and although they both claim to feel slightly improved, this may be primarily psychologic. Two other aneurysms of the ascending aorta were wrapped at the St. Louis City Hospitals in 1945, but these patients are believed to have died since that time without post-mortem examinations having been performed. One other aneurysm of the ascending aorta was explored at the Portland Veterans' Administration Hospital in 1947, but found unsuitable for wrapping because of erosion of the anterior chest wall to such a degree that cellophane could not be applied to the surface of the aneurysm. Several other patients have been considered unsuitable for surgery, either because of severe cardiac decompensation or complete obstruction of the left main bronchus by pressure from the aneurysm.

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*In consideration of the recent reports on the nonreactive nature of pure Polythene, I wish to stress that an impure film was used in the experimental and clinical results reported in this paper. This film was obtained from the Technical Service Laboratory of the Cellophane Division of the E. I. DuPont de Nemours and Company of Wilmington, Del., and contained no plasticizer or antioxidant material. Other substances were included in the film which were considered essential to the manufacturing process, the nature of which cannot be disclosed.

TABLE I. THE FINDINGS IN SIX PATIENTS WHOSE ANEURYSMS WERE WRAPPED WITH POLYTHENE CELLOPHANE

NO.	NAME	DATE	PLACE	TYPE	LOCATION	SYMPTOMS	RESULT
1	W. W.	7/6/45	Barnes Hosp., St. Louis, Mo.	Fusiform	Descending	Pain in anterior and posterior chest	Complete relief of pain
2	J. E.	12/8/45	Barnes Hosp., St. Louis, Mo.	Saccular and fusiform	Ascending aorta and innominate artery	Chest pain and weakness	Relief of pain, but weakness remains
3	F. K.	11/29/46	Good Samaritan Hosp., Portland, Ore.	Fusiform*	Distal arch and descending aorta	Chest pain and cough	Relief of chest pain
4	W. H.	1/16/47	Veterans' Hosp., Portland, Ore.	Fusiform	Distal arch and descending aorta	Chest pain	Complete relief of pain
5	J. L.	6/28/47	County Hosp., Portland, Ore.	Fusiform	Distal arch and descending aorta	Chest pain, hemoptysis, chronic cough, and dyspnea	
6	C. E.	7/10/47	Veterans' Hosp., Portland, Ore.	Saccular and fusiform	Ascending aorta	Anginoid pain on exertion	

*See Fig. 1.

COMMENTS

Although the chief purpose of cellophane wrapping of aneurysms is prophylactic and is intended to prevent their further expansion and eventual rupture or erosion into adjacent vital structures, it has been proved also to eliminate some of the already existing symptoms of aching and throbbing pain in the chest. As yet no pathologic material is available to determine whether or not an actual shrinking of the lumen occurs. However, the continued existence and improvement of symptoms in the four patients who have now been followed for two years would seem to indicate a reduction of expansion and pulsation in these individuals without any deleterious effects from undue constriction or obliteration of the lumen. The lack of decrease in size of the x-ray shadows is to be expected from the pathologic reaction noted in animals in which a thick layer of dense scar tissue is deposited on both sides of the cellophane.

The most favorable results have been obtained in fusiform aneurysms of the descending thoracic aorta (Fig. 1) where it is almost possible to encircle the dilatation completely without encountering other vital structures or major arterial

branches. The relief of the severe aching and throbbing pain produced by these lesions offers more comfort to the average syphilitic patient than the assurance that an asymptomatic aneurysm is no longer likely to grow larger or rupture.

At present, contraindications to surgery appear to consist of bronchial obstruction or erosion from pressure, severe heart disease with aortic insufficiency and decompensation, or erosion of the anterior chest wall. Arteriosclerotic aneurysms appear less suitable for surgical treatment than syphilitic aneurysms in view of the generalized distribution of the disease, advanced age of the patients, frequent location of the dilatation in the abdominal aorta with involvement of vital visceral branches, and frequently absent pulsation in the extremities.

Fig. 1.—Fusiform type of aneurysm of distal arch and descending aorta which has proved most suitable for cellophane wrapping to reduce chest pain (Patient 3, F. K.).

CONCLUSIONS

1. Polythene cellophane produces a dense fibrous tissue reaction which can be applied to aortic aneurysms to curb their pulsations, expansion, and tendency to rupture.

2. Six patients have been reported whose thoracic aortic aneurysms have been successfully treated by cellophane wrapping.

3. Relief of chest pain has been noted without deleterious effects from the cellophane during periods ranging from a few months to two years.

4. Indications and contraindications for surgical treatment of syphilitic intrathoracic aortic aneurysms have been mentioned.

5. The importance of selecting the proper type of cellophane to produce fibrosis cannot be emphasized too strongly, since certain varieties incite little or no foreign body reaction.

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THE MECHANISM OF IRREGULAR SINUS RHYTHM IN AURICULOVENTRICULAR HEART BLOCK

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IT HAS long been known that in auriculoventricular heart block, partial or complete, the auricles often exhibit an irregular rhythm. When such an irregularity exists, the auricular intervals which embrace ventricular systole are generally the shortest while those that follow in the wake of a ventricular systole are the longest. As illustrated in Figs. 1, 2, and 3, the irregularity is essentially a sinus arrhythmia, characterized by postsystolic slowing of the auricles. In these and subsequent figures and corresponding tables, auricular systole is indicated by the letter *P* and the initial graphic evidence of ventricular systole by the letter *Q*, no matter what its direction, negative or positive. Accordingly, *PQP* designates an auricular interval which contains the initial ventricular deflection and *P-P* designates an auricular interval devoid of such a deflection. Either the *PQP* or the *P-P* or both may contain a part or all of the terminal portion of the ventricular complex.

The point *Q* has been chosen because in a complete heart block, where QRS complexes are bizarre and wide, the peaks of R waves may be poorly defined and may not appear in the graph anywhere from 0.04 to 0.08 second after the onset of systole. Representing the initial deflection in the ventricular complex more accurately, the *Q* can serve as a point of reference from which measurements might be made in order to establish a time relation between the onset of ventricular systole and the onset of the initial and terminal P waves bounding intervals which contain it. Such time relations are designated in the tables as the *PQ* and *QP* segments of *PQP* intervals. As will be pointed out, a knowledge of the relative durations of these segments is important in determining the effect of ventricular systole, if any, upon the auricular pacemaker.

The pattern of the auricular irregularity in A-V heart block, although essentially a postsystolic slowing of the auricles, varies with the degree of the block In the first part of Fig. 1, for example, where a 3:1 partial block is illustrated, it will be observed that, although auricular cycle-lengths vary from beat to beat, they manifest an orderly, cyclic grouping in relation to ventricular systole. In each recurrent group of three cycles, beginning with an interval, *PQP*, which contains the initial ventricular complex (all of systole in this graph) the *PQP* interval is the shortest, the first *P-P* interval is the longest, and the cycle-length of the second *P-P* is intermediate. In a complete heart block as illustrated in Fig. 2, on the other hand, auricular rhythm may appear totally irregular be-

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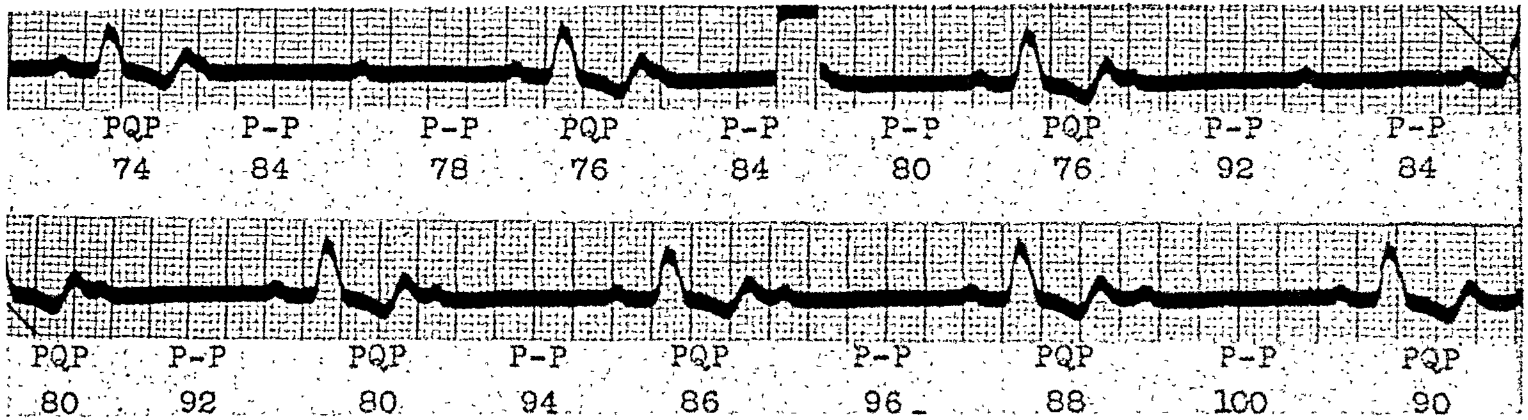

Fig. 1.—3:1 partial A-V heart block, changing abruptly to a 2:1 ratio. Auricular intervals irregular. However, *PQP* is always shortest; first *P-P* the longest; and second *P-P* (upper graph) is intermediate. Unit of measure = 0.01 second. (Graph corresponds to Cycles 22 to 39 in Table I.)

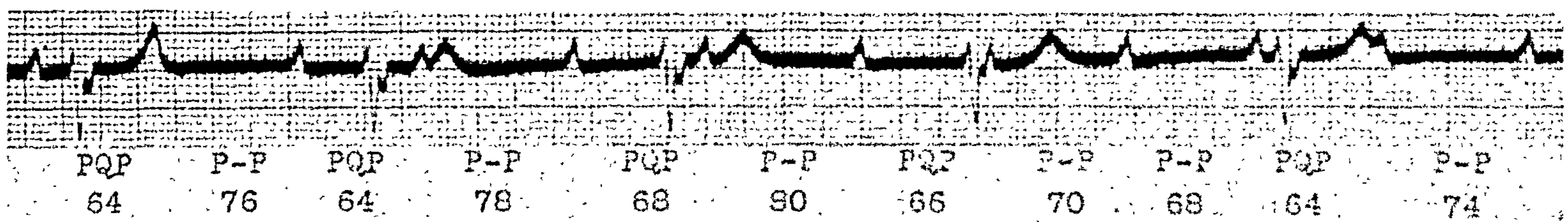

Fig. 2.—Complete A-V heart block. Ventricular rate, approximately 38.5 per minute. QRS-T interval, 0.52 second. Auricular intervals vary between 0.64 and 0.80 second. Note durations of second, fourth, and sixth postsystolic *P-P* intervals. Unit of measure, 0.01 second. (Graph corresponds to Cycles 6 to 10 in Table II.)

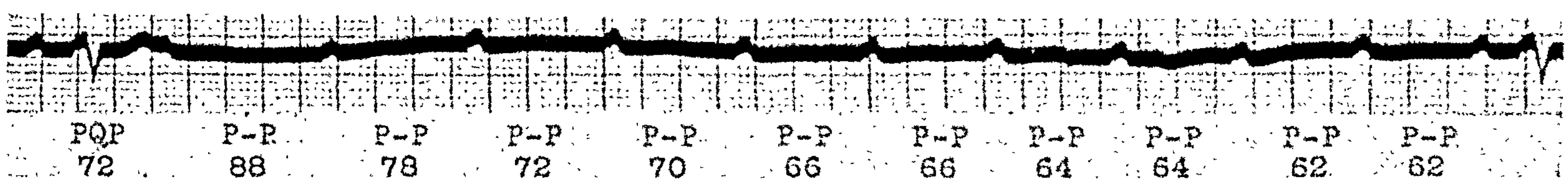

Fig. 3.—A span of ventricular standstill of 7.64 seconds' duration. Increase of first *P-P* over preceding *PQP* is more than 22 per cent. Slowing is then seen to vanish gradually over several cycles. Unit of measure, 0.01 second. (Graph corresponds to Cycles 10 to 29 in Table III.)

cause of dissociation between auricles and ventricles. Still another pattern appears in Fig. 3 where a ventricular standstill of 7.64 seconds is illustrated. In this figure, postsystolic slowing is seen to vanish gradually over a series of several cycles. These patterns are especially evident in Tables I, II, and III where measurements of the durations of *PQ* and *QP* segments, *PQP* and *P-P* intervals, first and subsequent ones, if any, are listed. The per cent increase of first *P-P* intervals over *PQP* intervals immediately preceding them are recorded in the last column of each table.

TABLE I. MEASUREMENTS OF THIRTY-NINE CONSECUTIVE AURICULAR INTERVALS IN A PARTIAL A-V HEART BLOCK, THE LAST EIGHTEEN OF WHICH ARE ILLUSTRATED IN FIG. 1. THE 3:1 A-V RATIO CHANGES ABRUPTLY, IN THE THIRTY-FIRST CYCLE TO A 2:1 RATIO. UNIT OF MEASURE, 0.01 SECOND

NO.	PQ	QP	PQP	P-P	% INCREASE
1	24	44	68		
2				80	17.65
3				72	
4	24	44	68		
5				80	17.65
6				72	
7	24	44	68		
8				76	11.76
9				72	
10	24	42	66		
11				82	24.24
12				74	
13	24	44	68		
14				80	17.65
15				72	
16	24	48	72		
17				84	16.67
18				76	
19	24	48	72		
20				84	16.67
21				80	
22	24	50	74		
23				84	13.51
24				78	
25	24	52	76		
26				84	10.53
27				80	
28	24	52	76		
29				92	21.05
30				84	
31	24	56	80		
32				92	15.00
33	24	56	80		
34				94	17.50
35	24	62	86		
36				96	11.63
37	24	64	88		
38				100	13.64
39	24	66	90		

PQ and *QP* are component segments of *PQP* intervals. Average duration of *PQP*, 0.74 second; of first *P-P* 0.86 second; of second *P-P*, 0.76 second. Average increase of first *P-P* over preceding *PQP* is approximately 16 per cent.

The auricular irregularity illustrated in the figures and tables is, we believe, peculiar to A-V heart block and will form the basis of our discussion. Coincidental irregularities such as premature beats, auricular flutter, and fibrillation, for example, are not included in this study. We are concerned with irregular sinus rhythms which, we believe, are related to and provoked by the circulatory dynamics of the heart block in which they are encountered. It is our purpose to establish a comprehensive concept to account for the physiologic mechanism of this arrhythmia.

TABLE II. MEASUREMENTS OF THIRTY-ONE CONSECUTIVE AURICULAR INTERVALS IN A COMPLETE A-V HEART BLOCK, CYCLES 6 TO 16 OF WHICH ARE ILLUSTRATED IN FIG. 2. UNIT OF MEASURE, 0.01 SECOND

NO.	PQ	QP	PQP	P-P	% INCREASE
1	64	8	72		
2				74	2.78
3				74	
4	4	64	68		
5				74	8.82
6	24	40	64		
7				76	18.75
8	38	26	64		
9				78	21.88
10	50	18	68		
11				80	17.65
12	56	10	66		
13				70	6.06
14				68	
15	12	52	64		
16				74	15.63
17	32	34	66		
18				80	21.21
19	42	28	70		
20				82	17.14
21	44	24	68		
22				78	14.71
23	56	14	70		
24				74	5.71
25	68	2	70		
26				70	0.00
27				68	
28	20	44	64		
29				76	18.75
30	36	30	66		
31				80	21.21

PQ and *QP* segments vary widely (dissociation). Auricular intervals, *PQP* and *P-P*, vary between 0.64 and 0.82 second. Average duration of first *P-P*, 0.76 second; of *PQP* 0.67 second; average increase of first *P-P* over *PQP*, approximately 13.5 per cent.

Irregular auricular action was first observed in experimental heart block in 1910 by Erlanger and Blackman[1] who assigned it to an increased vagal tone, enhanced by the arterial pulse. The first clinical case, that of a child suffering from Stokes-Adams seizures, was reported in 1914 by Hecht.[2] That the auricular arrhythmia tends to disappear on acceleration of the heart rate as a result of exercise or atropine administration was demonstrated by Wilson and Robinson[3]

in 1918. A decade later, Wenckebach and Winterberg[4] advanced the opinion that in A-V heart block improved nutrition of the sinoauricular node, as a result of ventricular systole, raises its potentiality for impulse production while impaired nutrition during ventricular diastole depresses the pacemaker. Aside from the foregoing views, there have been suggestions to the effect that the contracting ventricles might, by mechanical stimulation, enhance impulse production at the site of the normal pacemaker in a manner similar to what presumably occurs when premature auricular beats are provoked by mechanical stimulation of ectopic auricular foci during ventricular contractions in heart block. Accord-

TABLE III. MEASUREMENTS OF TWENTY-NINE CONSECUTIVE AURICULAR CYCLES IN A PARTIAL A-V HEART BLOCK WITH PERIODIC PROFOUND VENTRICULAR STANDSTILL. CYCLES 19 TO 29 ARE ILLUSTRATED IN FIG. 3. UNIT OF MEASURE, 0.01 SECOND

NO.	PQ	QP	PQP	P-P	% INCREASE
1	24	64	88		
2				92	4.54
3	24	56	80		
4				88	10.00
5	24	56	80		
6				90	12.50
7				80	
8				76	
9				74	
10	52	18	70		
11				74	5.71
12				72	
13	28	40	68		
14				70	2.91
15				68	
16	26	42	68		
17				76	11.81
18				72	
19	24	48	72		
20				88	22.22
21				78	
22				72	
23				70	
24				66	
25				66	
26				64	
27				64	
28				62	
29				62	

Cycle 5 initiates a ventricular standstill of 4.28 seconds; Cycle 19 initiates one of 7.64 seconds. During standstill, auricular slowing, most marked in first *P-P* intervals, vanishes gradually over several cycles.

ing to the observations of Wolferth and McMillan,[5] auricular premature beats, on the analogy of which this concept is based, cannot be satisfactorily explained on the assumption of mechanical stimulation of auricles by ventricles, but rather on the basis of retrograde conduction of the excitatory process through the area of block.

In recent years, it has become more and more apparent that a reflex vagus effect, as postulated by earlier observers, is a factor in the production of auricular

arrhythmia in A-V heart block. Graybiel and White,[6] for example, impressed with the fact that in ventricular standstill for two or more auricular cycles the one following ventricular systole is the longest while subsequent ones are of shorter duration, expressed the opinion that "under certain conditions ventricular systole increases vagal tone, possibly through the carotid sinus mechanism or directly through the arterial impulse in the sinoauricular artery or otherwise." They believed this was the usual mechanism. Shortly thereafter, but apparently independently, Kisch[7] came to a similar but more comprehensive conclusion. On the basis of a detailed study of a complete A-V block and in the light of the physiology of reflex vagus and accelerator effects upon the cardiac pacemaker, he postulated that a vagus-sympathetic reflex along aortic and carotid sinus pathways constitutes the mechanism responsible for postsystolic auricular slowing in A-V heart block. Recent observations of Fatzer[8] are in agreement with this opinion.

Apparently with a view to a critical appraisal of theories previously advanced, Parsonnet and Miller[9] reported observations in thirty-eight cases of heart block, twenty-eight complete and ten partial. They concluded that although each of the former theories "may embody factors" which, in part, account for the irregular auricular mechanism in heart block, "the reflex mechanism which is involved is unknown." Their criticism of "former theories" was based essentially on the following: (1) that they failed to account for the fact that the lengths of auricular intervals in heart block appeared to be "independent of the point of incidence of ventricular systole"; and (2) that they failed to explain "exceptions to the rule," namely, cases in which an auricular interval containing the initial ventricular complex (*PQP*) is longer than an adjacent interval devoid of such a complex (*P-P*); or cases in which there is "no correlation at all" between these two types of auricular intervals. Since in the light of their criticsm no former theory fully accounted for the auricular irregularity encountered in heart block, these authors suggested that the length of auricular intervals during ventricular diastole in heart block might be determined by the relative dominance of two opposing forces. One of these is a depression of the pacemaker as a result of the "absence of the stimulus from the contracting ventricle"; the other, a Bainbridge reflex.

We take no exception to the foregoing criticism as far as it concerns the view advanced by Wenckebach and Winterberg. This is untenable, on the whole, because it is contrary to the known fact that auricular slowing in heart block generally occurs in the wake of an effective ventricular contraction when cardiac nutrition is presumably at its best. If one assumes, however, that auricular arrhythmia when present is due to a reflex vagus effect, the criticism does not apply. The fact that auricular irregularity is not always present and that when it is present a clear-cut correlation between auricular cycle-length and the point of incidence of ventricular systole is not readily demonstrable does not mitigate against the concept that in A-V heart block the auricular pacemaker is under the influence of a reflex vagus mechanism. Such a mechanism is labile, subject to many intrinsic and extrinsic factors, and since its influence

usually endures over several auricular cycles its effects are often obscured. Even the degree of the heart block may obscure it.

In complete heart block, for example, the rhythm of the auricles may appear so irregular as to create the impression of an utter lack of correlation. However, this seeming total irregularity is precisely what might be deemed to serve as evidence of correlation. Since in complete dissociation auricular contraction may precede, coincide with, or follow auricular contractions, the degree of ventricular effect upon auricular cycle-lengths, if any, must be highly variable. Careful measurements of *QP* segment-lengths and subsequent *P-P* cycle-lengths are required to demonstrate the influence of ventricular systole upon the auricular rhythm.

The degree of ventricular effect upon an auricular interval would depend, in part at least, upon the element of time during which ventricular influence effectively operates. The condition for an optimal effect would clearly be a *QP* time relationship which would permit ventricular systole to exert its maximal influence upon the early phase of the next impulse production period at the S-A node and thus delay the terminal P wave of the postsystolic *P-P* interval, as indicated in the pattern, (P.....*Q.P*...........P). A lesser ventricular effect would be represented by a pattern in which the Q is not quite so close to the first P wave of the P-P interval, (P....*Q*...*P*........P). By the same token, *PQP* intervals should themselves be least affected unless the Q appears very early in the interval, in which case the ventricular effect would be exerted largely upon the terminal P of the *PQP* and to a lesser degree upon the next *P-P* interval, (P.*Q*.......*P*.......P). Such patterns depicting the relationship between *QP* segment-lengths and auricular cycle-lengths we have repeatedly observed as conspicuous features of the auricular irregularity which accompanies A-V heart block. Such observations have led us to believe that the variation in auricular cycle-length which constitutes the auricular arrhythmia is, in part at least, a function of the point of incidence of ventricular systole.

Fig. 4 illustrates these features. Four of the eleven auricular cycles illustrated, namely, Cycles 3, 5, 8, and 10, are *P-P* intervals. Their respective cycle-lengths are 1.04, 1.00, 1.08, and 0.96 second. As listed in Table IV,*A*, the *QP* segments preceding the two longer cycles, 3 and 8, are relatively short, 0.10 and 0.18 second, respectively; while *QP* segments which precede the two shorter cycles, 5 and 10, are relatively long, 0.48 and 0.56 second. The fact that short *QP* segments are followed by long *P-P* intervals and long *QP* segments by short *P-P* intervals suggests that the duration of *P-P* intervals and the duration of the *QP* segments within *PQP* intervals immediately preceding them are related by an inverse ratio. Examination of large numbers of consecutive auricular cycles actually bears this out and tends to suggest, furthermore, that in a measure the relationship is a quantitative one.

Revealing in this connection is an analysis of Table IV in which measurements of three consecutive electrocardiograms, *A*, *B*, and *C*, are recorded from the same patient, representing a total of 128 auricular cycles. It will be recalled that the first eleven cycles of Tracing *A* are illustrated in Fig. 4. Of these 128

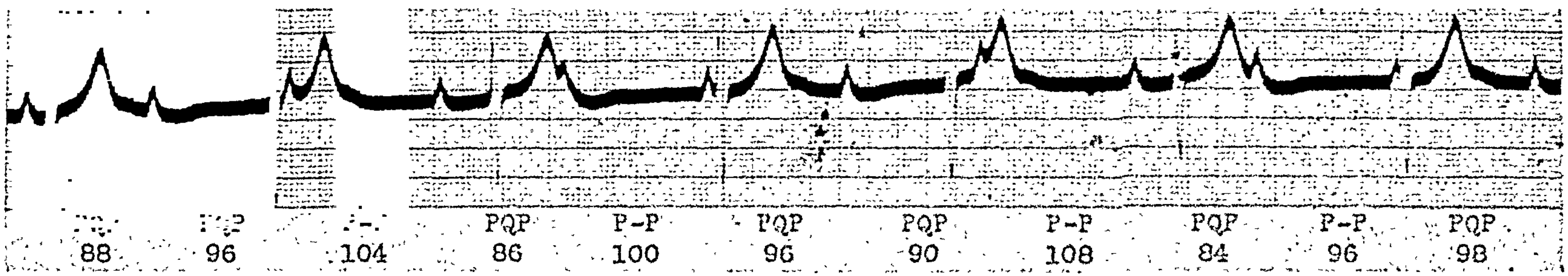

Fig. 4.—Complete A-V heart block. Ventricular rate approximately 38.5 per minute; QRS-T = 0.52 second. Auricular intervals totally irregular.

P-P intervals which follow close in the wake of ventricular systole, Cycles 3 and 8, are longer; those farther removed from ventricular systole, Cycles 5 and 10, are shorter. The one farthest removed, Cycle 10, is the shortest.

Note the exceptions to the rule implied in these *PQ* relationships: (1) The *P-P* in Cycle 3, although closest to ventricular systole, is not the longest; (2) Cycle 11, although a *PQP*, is longer than the preceding *P-P*.

Optimal *QP* segments for maximal ventricular effects are discussed in the text. (Graph corresponds to Cycles 1 to 11 in Column *A* of Table IV.)

auricular cycles, seventy-three are *PQP* intervals. There are six cycles which either terminate or begin with merged auricular and ventricular complexes in which the P wave is obscured by the QRS. These are designated as *PQ* or *QP* intervals and will not be considered.

The remaining forty-nine auricular cycles are *P-P* intervals. On viewing the table, it is at once apparent that although the durations of these vary to a wide degree, they are, on the whole, appreciably longer than the duration of the *PQP* intervals which precede them. The average duration of the forty-nine *P-P* intervals is approximately 0.99 second while the average duration of forty-nine *PQP* intervals immediately preceding them is approximately 0.87 second. The average increase of *P-P* intervals over their preceding *PQP* intervals is approximately 14 per cent.

More interesting is the fact that when the forty-nine *P-P* intervals are broken down into subgroups on the basis of cycle-lengths and the average *QP* segments in the preceding *PQP* intervals are calculated for each subgroup, a quantitative inverse relationship of *P-P* cycle-length to preceding *QP* segment-lengths is noted. Of the forty-nine *P-P* cycles contained in the three sections of Table IV, there are twenty-three whose cycle-lengths are 0.98 second or less, the average being 0.95 second. The average duration of *QP* segments preceding this subgroup is approximately 0.47 second. The cycle-lengths of the remaining twenty-six *P-P* intervals measure 1.00 second and over, the average being slightly above 1.02 seconds. The average duration of *QP* segments preceding these longer *P-P* intervals is less than 0.23 second. Since the average duration of the twenty-six longer *P-P* intervals was approximately 1.02 seconds, all *P-P* intervals with cycle-lengths of 1.02 seconds and over were further analyzed. Of these, the table contains fifteen with cycle-lengths ranging between 1.02 and 1.08 seconds, the average being approximately 1.04 seconds. The average *QP* segment preceding these longest P-P intervals is only 0.17 second.

An analysis of Table IV confirms, then, what has been suggested by its corresponding Fig. 4. The table discloses not only that *P-P* intervals, on the whole, are longer than the *PQP* intervals which precede them, but also that the shorter the *QP* segment within a systolic *PQP* interval, the longer is the duration of the subsequent diastolic *P-P* interval and that, therefore, these two variables are related by a quantitative inverse ratio. This analysis convincingly demonstrates that the time-segment, *QP* which elapses between the onset of ventricular systole and the onset of the auricular systole which signals the beginning and constitutes the initial boundary of the next *P-P* interval, is a factor in determining the duration of that interval.

Observations such as these have led us to support the view that postsystolic auricular slowing in A-V heart block, when present, is the result of a reflex vagus effect initiated by the arterial pulse. The physiologic mechanism proposed is that of a reflex inhibition of the auricular pacemaker, initiated by a pressure rise within the aorta and carotid arteries incident to the systolic injection of these vessels. Such an aortic and carotid sinus reflex alone, it would seem, could account for the fact that auricular slowing in heart block generally

TABLE IV. MEASUREMENTS OF THREE CONSECUTIVE ELECTROCARDIOGRAMS A, B, AND C, IN A COMPLETE A-V HEART BLOCK, COMPRISING A TOTAL OF 128 AURICULAR CYCLES. CYCLES 1 TO 11 OF TRACING A ARE ILLUSTRATED IN FIG. 5

NO.	A					NO.	B					NO.	C				
	PQ	QP	PQP	P P	% INCR.		PQ	QP	PQP	P-P	% INCR.		PQ	QP	PQP	P-P	% INCR.
1	16	72	88			1	8	90	98			1	22	62	84		
2	86	10	96			2	68	22	90			2				92	9.52
3				104	8.33	3				108	20.00	3	4	80	84		
4	38	48	86			4	28	58	86			4	72	16	88		
5				100	16.28	5	98					5				98	11.36
6	10	86	96			6		98				6	40	42	82		
7	72	18	90			7	58	32	90			7				84	2.44
8				108	20.00	8				100	11.11	8	24	52	76		
9	28	56	84			9	26	62	88			9				92	21.05
10				96	14.29	10				94	6 82	10	8	76	84		
11	6	92	98			11	4	86	90			11	76	12	88		
12	66	24	90			12	68	18	86			12				104	18.18
13				104	15.56	13				102	18.60	13	36	48	84		
14	30	54	84			14	32	52	84			14				100	19.05
15				96	14.29	15				96	14 29	15	8	80	88		
16	6	90	96			16	8	80	88			16	80	12	92		
17	68	20	88			17	72	14	86			17				108	17.39
18				104	18.18	18				102	18.60	18	36	52	88		
19	32	54	86			19	36	48	84			19				100	13.64
20				98	13.95	20				96	14 29	20	12	76	88		
21	6	90	96			21	14	70	84			21	84	8	92		
22	68	20	88			22	80	6	86			22				102	10.86
23				102	15.91	23				100	16.29	23	44	42	86		
24	34	52	86			24	44	42	86			24				96	11.63
25				98	13 95	25				98	13.95	25	20	64	84		
26	10	76	86			26	16	68	84			26				92	9 52
27	80	8	88			27	84	8	92			27	4	84	88		
28				102	15.91	28				100	8.70	28	72	14	86		
29	44	44	88			29	44	42	86			29				96	11.63
30				102	15.91	30				98	13.95	30	28	56	84		

31	12	74	86			31	60	24	84			31				94	11.90
32	82	6	88			32	88	4	92			32	20	62	82		
33				98	11.36	33				100	8.70	33				92	12.20
34	52	34	86			34	44	40	84			34	8	80	88		
35				102	18.60	35				100	19.05	35	76	12	88		
36	22	62	84			36	20	64	84			36				100	13.64
37	96					37	94										
38		96				38		94									
39	60	28	88			39	52	32	84								
40				104	18.18	40				96	14.29						
41	24	60	84			41	28	56	84								
42				94	11.90	42				96	14.29						
43	4	96	100			43	4	84	88								
44	58	30	88			44	68	16	84								
45				100	13.64	45				100	19.05						
						46	38	46	84								
						47				96	14.29						

Columns A, B, and C contain a total of forty-nine *P-P* intervals. Their average duration is 0.99 second. Average duration of forty-nine *PQP* intervals immediately preceding them is 0.87 second. Average increase of *P-P* over preceding *PQP* is approximately 14 per cent.

An analysis of this table reveals a quantitative relationship between *QP* segment-lengths and subsequent *P-P* cycle-lengths. See text.

appears in cycles immediately following ventricular systole and for the fact that during longer periods of ventricular standstill, the slowing vanishes gradually over a succession of several cycles. This alone could account for the fact, furthermore, that the durations of *P-P* intervals are influenced and, in a measure, determined by the proximity of adjacent ventricular complexes.

The physiologic basis of an hypothesis which assumes that the mechanism underlying diastolic auricular slowing in heart block is an aortic-carotid sinus reflex is in keeping with known facts about the function of the cardiac vagus-sympathetic nerves and the mechanism of reflex cardiac inhibition. Normally, the tone of the vagus nerves is known to depend to a significant degree upon the pressure within the aorta and carotid arteries.[10] Increase of pressure within these vessels raises vagus tone, on the one hand, and, on the other, tends to lower the tone of its sympathetic antagonists. Decrease of pressure produces the opposite effect.[11,12] Reflex inhibition of the heart is a well-known phenomenon and the fact that striking alterations in vagal tone may occur as a result of single effective ventricular beats has been demonstrated clinically[7] and experimentally.[13] Based upon well-known properties of the cardiac vagus-sympathetic nerves and upon equally well-known hemodynamic events that accompany ventricular systole, the deduction that auricular irregularity in A-V heart block, as represented in the foregoing figures and tables, is the result of a vagus effect and that an aortic-carotid sinus reflex, initiated by ventricular systole, constitutes the underlying mechanism would seem reasonable.

It is realized, of course, that before such an hypothesis may be deemed valid, two conditions must be satisfied. First, since it assumes that auricular slowing in heart block is a function of vagus tone, it remains to be demonstrated that drugs which reduce vagus effect would tend to eliminate differences in cycle-lengths of *PQP* and *P-P* intervals. Second, since it assumes also that the vagus effect is initiated by a systolic rise in arterial pressure incident to ventricular systole, it remains to be demonstrated that ventricular systole is an essential component of the reflex mechanism and that slowing of the auricles does not appear in the wake of hemodynamically ineffective ventricular systoles.

To meet the first requirement, a case of complete heart block was observed under the influence of atropine. The drug was administered intramuscularly (grain 1/50) and electrocardiograms were taken before and during its effects. In order to produce magnified and clearly defined P waves with sharp summits and thus facilitate measurements, graphs were taken with right arm-chest leads and the sensitivity of the instrument was increased to a 2 cm. deflection for a millivolt. The graphs are illustrated in Fig. 5 as: *A*, before atropine; *B*, three to five minutes after; and *C*, one-half hour after atropine. As indicated in their legends, the graphs in these figures are sections of corresponding electrocardiograms containing 34, 35, and 33 consecutive auricular cycles, respectively, whose measurements are detailed in Table V *A*, *B*, and *C*.

The electrocardiogram taken *before atropine*, illustrated in Fig. 5,*A*, presents features already discussed for this type of graph. The durations of *P-P* intervals, for example, exceed those of *PQP* intervals preceding them and the longer *P-P*

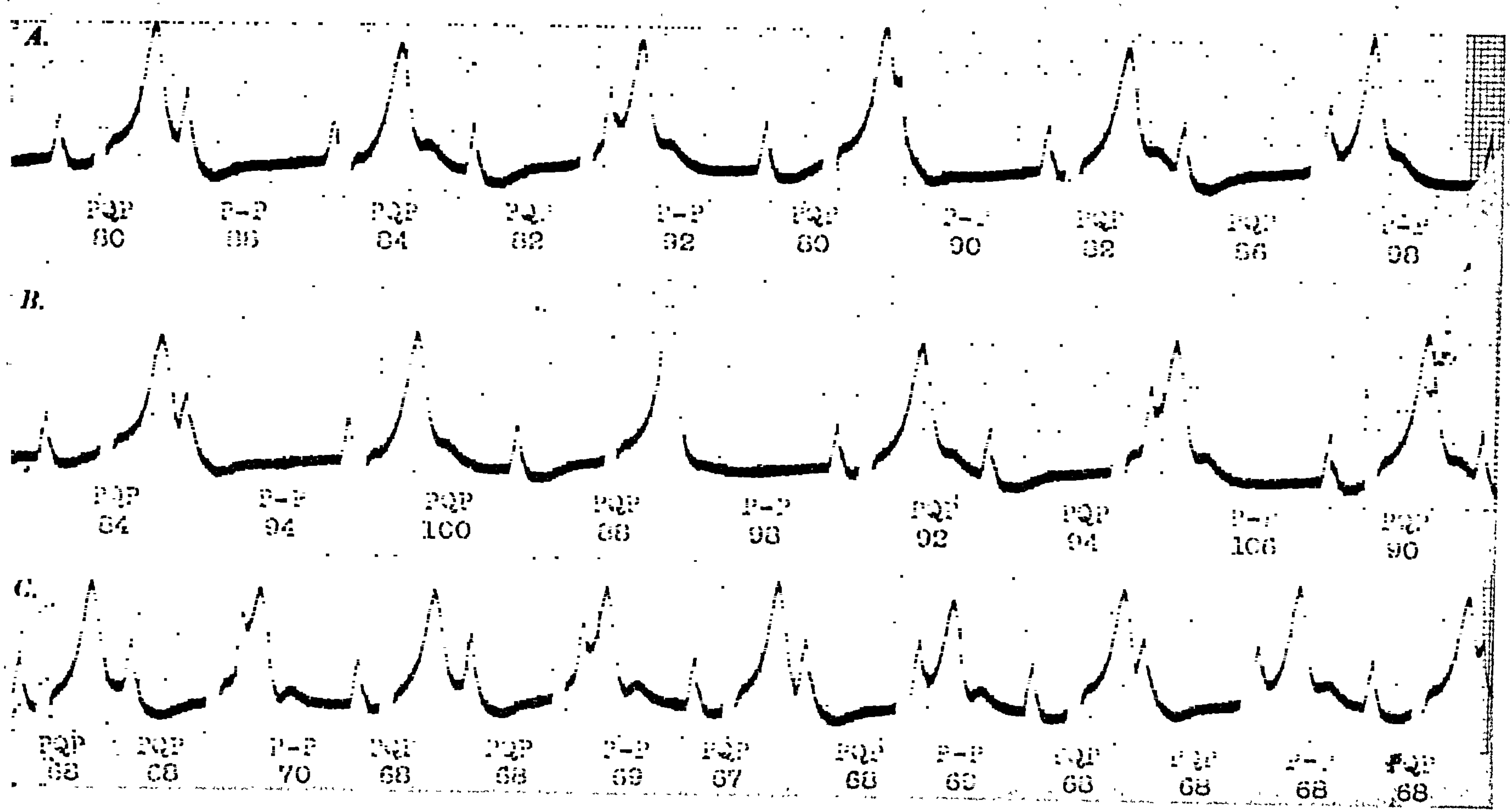

Fig. 5.—Effect of atropine on auricular irregularity in A-V heart block. Chest Lead CR_1; deflection 2.0 centimeters. Descending limb of QRS not illustrated. Unit of measure, 0.01 second.

A, before atropine. Ventricular intervals, 1.46 to 1.48 seconds. QRS-T, 0.50 second. Auricular intervals variable. As illustrated in Cycles 2, 5, 7, and 10, *P-P* cycle-lengths are related to *QP* segment-lengths. (Graph corresponds to Cycles 10 to 19 in Column *A* of Table V.)

B, three to five minutes after atropine. Ventricular intervals and QRS-T, approximately the same as in *A*. Auricular intervals are longer and highly variable (0.84 to 1.06 seconds). Note increase of *P-P* cycle-lengths as *QP* segment-lengths decrease. In Cycle 2 where initial P is on downstroke of T, *P-P* = 0.94 seconds. In Cycle 5 where initial P is at peak of T wave, *P-P* = 0.98 second. In Cycle 8 where initial P is on upstroke of T, *P-P* = 1.06 second. (Graph corresponds to Cycles 6 to 14 in Column *B* of Table V.)

C, one-half hour after atropine. Ventricular intervals, 1.08 seconds. QRS-T, 0.46 second. Range of auricular cycle-lengths, 0.67 to 0.70 second. For the most part, variations do not exceed 0.01 second. (Graph corresponds to Cycles 15 to 27 in Column *C* of Table V.)

intervals appear in the wake of comparatively short *QP* segments. As compiled from Table V,*A*, the average duration of first *P-P* intervals is approximately 0.93 second and the average duration of *PQP* intervals preceding them is 0.83 second. The increase of the former over the latter is approximately 11.5 per cent.

Graphs taken *three to five minutes after atropine*, illustrated in Fig. 5,*B*, manifest the initial, transient, vagotropic effect of the drug. The auricles are slower and the range of their cycle-lengths are greater. The three *P-P* intervals illustrated, namely, Cycles 2, 5, and 8, measure successively 0.94, 0.98, and 1.06 seconds, and, as shown in Table V,*B*, the *QP* segments within the *PQP* intervals preceding them are 0.46, 0.32, and 0.14 second, respectively. The progressive increase in *P-P* cycle-length which accompanies the gradual decrease in *QP* segment-length is strikingly illustrated in this figure. The inverse time relationship between *P-P* cycle-length and *QP* segment-length stands out conspicuously throughout Table V,*B*. The durations of *P-P* intervals vary, for example, between 0.94 and 1.06 seconds, their average being approximately 1.00 second. All *P-P* intervals which have cycle-lengths equal to or exceeding this average are preceded by short *QP* segments, 0.18 second or less.

At this point, attention is called to the third auricular interval in Fig. 5,*B*, which corresponds to Cycle 8 in Table V,*B*. Although this is a *PQP*, its duration, 1.00 second, not only exceeds all other *PQP* intervals but is, in fact, equal to the average duration of the *P-P* intervals in the table. This is the "exception to the rule" of which much has been made in some of the literature. If viewed, however, in the light of a reflex vagus effect, conditioned by the point of incidence of ventricular systole, this exception is understandable. Since in this *PQP* the initial ventricular complex is very close to the first P wave (P.Q.......P), there is adequate time for the operation of a relatively effective reflex which, because of this element of time and the increased sensitivity of the reflex mechanism as a result of the initial vagotropic effect of atropine, can appreciably delay the second P wave of the interval.

About *one-half hour after atropine*, an auricular rate of 88 a minute was attained. As illustrated in Fig. 5*C* and recorded in Table V*C*, even this limited vagoparalytic effect of the drug practically eliminated the differences between *PQP* and *P-P* cycle-lengths. According to the table, the average *PQP* measures 0.675 second while the average duration of *P-P* intervals is 0.687 second. The difference, approximately 0.01 second, is well within the range of error of computation. Although there are a few instances in the table where *P-P* exceeds *PQP* by 0.02 second, there are long periods where the durations of the two are identical (Cycles 24 to 33 in Table V *C*).

The illustrations in Fig. 5 and the measurements listed in Table V amply demonstrate that the vagoparalytic effect of atropine, although only moderate in this case, tends, nevertheless, to eliminate the auricular irregularity manifested by differences in *P-P* and *PQP* cycle-lengths in A-V heart block. Consequently, the observation supports the view that vagus tone is a factor in producing the irregularity and satisfies one of the requirments set forth as es-

TABLE V. MEASUREMENTS OF THREE CONSECUTIVE ELECTROCARDIOGRAMS IN A CASE OF COMPLETE A-V HEART BLOCK TO DEMONSTRATE THE EFFECTS OF ATROPINE ON THE AURICULAR RHYTHM. CYCLES IN BRACKETS ARE ILLUSTRATED IN CORRESPONDING FIGS. 5 *A*, *B*, AND *C*.

NO.	A: BEFORE ATROPINE					NO.	B: THREE TO FIVE MINUTES AFTER					NO.	C: HALF-HOUR AFTER				
	PQ	QP	PQP	P-P	% INCR.		PQ	QP	PQP	P-P	% INCR.		PQ	QP	PQP	P-P	% INCR.
1	68	14	82			1	54	30	84			1	42	24	66		
2				94	14.63	2				98	16.67	2				67	1.52
3	36	44	80			3	20	64	84			3	10	57	67		
4				92	15.00	4	86	8	94			4	44	23	67		
5	12	68	80			5				104	10.64	5				68	1.49
6	76	8	84			6	38	46	84			6	12	56	68		
7				86	2.38	7				94	11.90	7	46	20	66		
8	54	26	80			8	8	92	100			8				68	3.03
9				92	15.00	9	56	32	88			9	12	56	68		
10	25	54	80			10				98	11.36	10	46	22	68		
11				88	10.00	11	18	74	92			11				70	2.94
12	6	78	84			12	80	14	94			12	14	54	68		
13	70	12	82			13				106	12.77	13	48	20	68		
14				92	12.20	14	26	64	90			14				69	1.47
15	38	42	80			15	84	12	96			15	12	56	68		
16				90	12.50	16				106	10.42	16	52	16	68		
17	14	68	82			17	30	58	88			17				70	2.94
18	80	6	86			18	90	8	98			18	18	50	68		
19				98	13.95	19				104	6.12	19	56	12	68		
20	44	40	84			20	38	48	86			20				69	1.47
21				94	11.90	21	96					21	22	45	67		
22	12	76	88			22		100				22	60	8	68		
23	74	16	90			23	50	38	88			23				69	1.47
24				98	8.88	24				96	9.09	24	26	42	68		
25	34	50	84			25	14	74	88			25	62	6	68		
26	94					26	80	10	90			26				68	0.00
27		94				27				100	11.11	27	28	40	68		
28	60	26	86			28	32	54	86			28	64	4	68		
29				94	9.30	29	94					29				69	1.47
30	20	62	82			30		104				30	28	40	68		
31	90					31	44	44	88			31	68				
32		92				32				96	9.09	32		68			
33	50	32	82			33	48	42	90			33	32	36	68		
34				92	12.20	34	70	18	88								
						35				100	13.64						

A, range of auricular cycle-lengths, 0.80 to 0.98 second. Average duration of *P-P*, 0.93 second; of *PQP* preceding them, 0.83 second.

B, range of auricular cycle-lengths, 0.84 to 1.06 seconds. Average duration of *P-P*, 1.00 second; of preceding *PQP*, 0.90 second. All *P-P* intervals of 1.00 second or over are preceded by *QP* segments of 0.18 second or less.

C, range of auricular cycle-lengths, 0.67 to 0.70 second. Average duration of *P-P* intervals, 0.687 second; of preceding *PQP*, 0.675 second. Note uniformity of Cycles 24 to 33 where nine out of ten cycle-lengths = 0.68 second.

sential to the validity of an hypothesis which holds that an aortic-carotid sinus reflex is the underlying physiologic mechanism of the auricular irregularity which accompanies A-V heart block.

It will be recalled in this connection that still another condition was to be satisfied. Since it has been assumed that the reflex mechanism is initiated by a systolic rise in arterial pressure incident to ventricular systole, it was to be demonstrated that a hemodynamically effective ventricular systole is an essential component of the reflex mechanism. Actually, observations presented so far lend considerable support in this direction. Ventricular systole has been repeatedly implicated as a factor in determining the degree of pacemaker inhibition. This has been amply demonstrated by the analysis of subgroups in Table IV and confirmed by Fig. 5,*B* and Table V,*B* which illustrate the vagotropic effects of atropine.

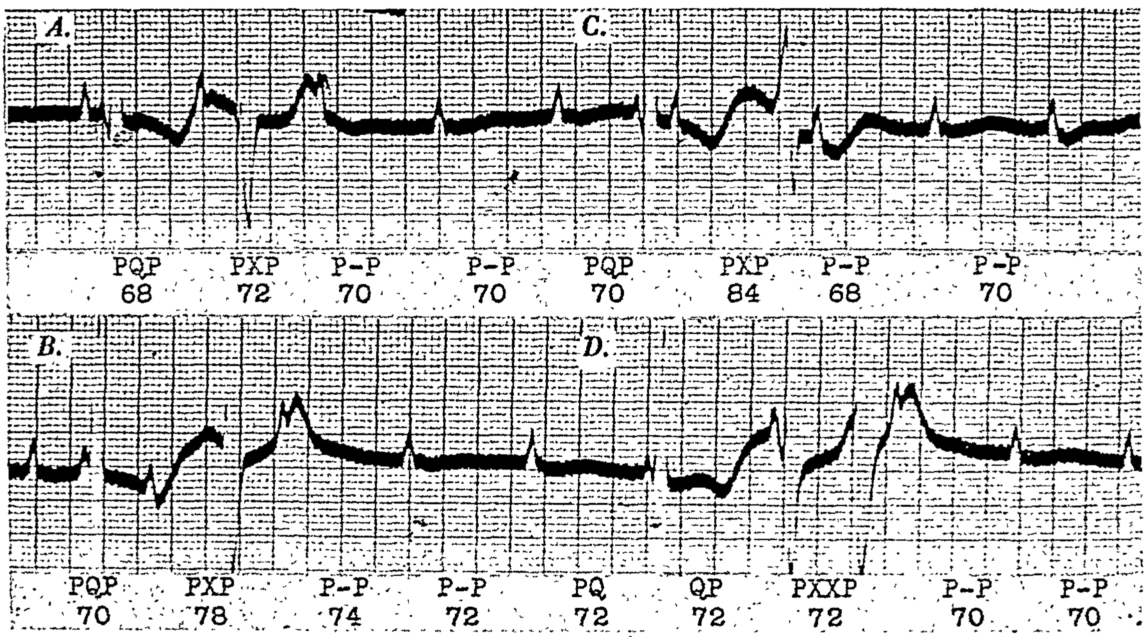

Fig. 6.—The gradual decrease, through Sections *A*, *B*, and *C*, of segments Q to P_1 is accompanied by a proportional increase in the duration of postsystolic auricular intervals, *PXP*. Although there is a similar decrease of segments X to P_2, the durations of postextrasystolic intervals *P-P* are not appreciably affected. In Section *D*, the segment Q to P_1 being very long, the duration of *PXP* is not altered. The next interval *P-P*, although in the wake of two extrasystoles, is also unaffected.

It is reasonable to assume that ventricular systole initiates the reflex vagus mechanism by way of a hemodynamic impulse. The large stroke volume which follows prolonged diastoles in A-V heart block can effectively stimulate the carotid sinus and aortic depressor nerves and thus set in motion the reflex which leads to inhibition of the auricular pacemaker. In order to demonstrate the role of this hemodynamic factor as the vis a tergo which provokes the reflex mechanism, a case of complete A-V heart block acccompanied by transient bigeminal and trigeminal rhythms due to ventricular premature beats was studied with a view to determining the relative effects of normal and premature ventricular

systoles upon *auricular intervals which follow in their wake*. This case affords an opportunity for a parallel study of the relative inhibitory effects of two types of ventricular systoles in the same subject.

As illustrated in Fig. 6 and detailed in Table VI, normal ventricular systoles in this case influence the durations of auricular intervals which follow in their wake in accordance with a rule already stated and repeatedly exemplified. The duration of these postsystolic auricular intervals, *PXP* (so designated because they contain an extrasystole), varies inversely with the duration of *QP* segments preceding them. In the four groups of complexes illustrated, *A*, *B*, *C*, and *D*, each beginning with a *PQP* interval, these variations in *QP* segment-lengths and *PXP* cycle-lengths, as well as in the percentage increase of postsystolic *PXP* over systolic *PQP* intervals, are striking. It will be noted, however, that although the durations of first postsystolic auricular intervals, *PXP*, are clearly influenced by the duration of the QP segments of normal ventricular systoles preceding them, second auricular intervals, *P-P*, which follow in the wake of extrasystoles, single or coupled, are not similarly affected. The time, *XP*, which elapses between the initial deflection of the premature ventricular systole and the initial P wave of the auricular interval which follows does not influence the duration of that interval. This holds true, in this case, no matter what the duration of the *XP* segment, and no matter what degree of inhibition the preceding normal systole had produced.

TABLE VI. MEASUREMENTS IN SECTIONS A, B, C, AND D OF A COMPLETE A-V HEART BLOCK WITH BIGEMINAL AND TRIGEMINAL RHYTHMS TO DEMONSTRATE THE RELATIVE INHIBITORY EFFECTS OF NORMAL AND PREMATURE VENTRICULAR SYSTOLES UPON THE AURICULAR PACEMAKER. UNIT OF MEASURE, 0 01 SECOND

SECTION	NO.	PQ	QP	PQP	PX	XP	PXP	% INCR.	P-P
A	1	14	54	68					
	2				24	48	72	5.88	
	3								70
	4								70
B	1	30	40	70					
	2				46	32	78	11.43	
	3								74
	4								72
C	1	48	22	70					
	2				60	24	84	20.00	
	3								68
	4								70
D	1	72?							
	2		72?						
	3				8	64	72	0.00	
	4								70
	5								70

PX and *XP* are component segments of auricular intervals *PXP* which follow in the wake of normal systole. *P-P* intervals, first and second, are those that follow in the wake of premature systoles.

In Section *D*, *PQ* and *QP* represent two whole auricular intervals. The P wave, terminal to the first and initial to the second interval, is obliterated by the QRS (see Fig. 6).

In each section, compare relative duration of *QP* and *PXP* with those of *XP* and *P-P*.

The marked contrast in the inhibitory effects of two different types of ventricular systoles in the same subject clearly indicates that an effective hemodynamic impulse is an essential component of the reflex vagus mechanism in A-V heart block. For, as has been demonstrated, when ventricular systole is normal and stroke volume seemingly adequate, *QP* segments are selective and when optimal, are followed by conspicuous slowing of the auricles. In the case of extrasystoles, on the other hand, there is no optimal *XP* segment for the obvious reason that extrasystoles, when hemodynamically ineffectual, lack the stroke volume necessary to provoke a reflex inhibition of the auricular pacemaker. These observations satisfy the second condition set forth as essential to the validity of an hypothesis which holds that an aortic-carotid sinus reflex, initiated by a rise in pulse pressure incident to ventricular systole, is the physiologic mechanism of the auricular irregularity which accompanies auriculoventricular heart block.

In the final appraisal of such a mechanism, certain seeming inconsistencies in auricular response to ventricular systole must be taken into account. Why, for example, is auricular irregularity conspicuous in some but only slight or even negligible in other cases of A-V heart block? Why is a short *QP* segment in the electrocardiogram of one subject an optimal condition for maximal postsystolic auricular slowing, while a longer *QP* range is optimal for another subject? Answers to these questions are implicit in the hypothesis of a reflex vagus mechanism, the properties of which are inherent in and peculiar to individuals. Clearly such properties of a reflex as its intensity, its latent period, or both, are themselves conditioned by certain intrinsic and extrinsic factors, apart from the initial force which provokes the reflex. In terms of an aortic-carotid sinus reflex, for example, the following may be regarded as intrinsic factors for a given subject: age, resiliency of arteries, blood pressure, and pulse rate; sensitivity of the aortic and carotid sinus receptor nerves, the vagus center, the vagus nerve and its myoneural junctions; and the nutritional state and the anatomic and physiologic integrity of the sinoauricular node. These, in the aggregate, determine the intensity and the latency of the reflex. There are other factors, more remote and extrinsic, whose effects on the vagus mechanism are transient and unpredictable. Pulmonary and gastrointestinal reflexes, pain, anxiety, and other emotional factors belong to this category.

In the realization, then, that a variety of intrinsic and extrinsic factors condition the properties of a vagus mechanism in a given subject, seeming inconsistencies regarded by some as mitigating against the concept of a reflex vagus effect upon the auricular pacemaker actually serve to support it. For only a mechanism subject to so many influences can account for the wide variations in the degree of auricular slowing encountered. Differences in reflex intensity, for example, would clearly account for the fact that not all cases of A-V heart block exhibit significant postsystolic slowing of the auricles. Differences in reflex latency, on the other hand, would explain why maximal slowing appears soon after ventricular systole in some, while in others, ventricular effect is considerably delayed. The electrocardiogram detailed in Table V, *B*, for example, where the computed optimal *QP* range is 0.08 to 0.18 second (average, 0.12

second) was recorded in the case of a 21-year-old man under the influence of the initial vagotropic effects of atropine. The electrocardiogram, the measurements of which are listed in Table II where the optimal *QP* segment range is 0.18 to 0.44 second, (average, 0.30 second), was recorded in a 55-year-old man with arteriosclerotic heart disease. As the tables show, reflex intensity was high in both cases; reflex latency, on the other hand, was significantly different.

Any discussion of the latent period of a cardiac inhibitory reflex is beset with difficulties, not so much because of the complexity of the reflex arc but rather because the reflex involves a structure, the sinoauricular node, the physiology of which, as far as impulse production and impulse discharge are concerned, is not well known. Biologic processes, as a rule, are not linear but exponential functions. It is safe to assume, therefore, that for an effective inhibition of the auricular pacemaker the height of a reflex vagus effect would have to correspond to the early phase of impulse production. According to Ashman and Gouaux,[13] about 0.11 second elapses between the appearance of the initial ventricular complex in the electrocardiogram and the first evidence of the mechanical effects of ventricular systole upon the aortic and carotid sinus nerves. Since another 0.01 second is required for the completion of the reflex, these observations suggest that a reflex vagus effect on the sinoauricular node should appear approximately 0.12 second after the initial ventricular deflection. Kisch and Zucker,[14] in a study of a complete heart block in which there were evidences of sinoauricular block in the wake of ventricular systole, found a range of 0.13 to 0.39 second as optimal for the elimination of a sinus P wave. The variations in reflex response indicated in these reports correspond to our findings in the two cases cited. They are consistent with the mechanism of a reflex vagus effect, the behavior of which is conditioned by a variety of intrinsic and extrinsic factors peculiar to individual subjects.

SUMMARY

In auriculoventricular heart block, the rhythm of the auricles is often irregular. Illustrative electrocardiograms are presented to demonstrate patterns of this irregularity as they appear in partial and complete A-V heart block. The literature dealing with the mechanism of the auricular irregularity has been reviewed.

Measurements of large numbers of consecutive auricular intervals and their component segments in electrocardiograms of A-V heart block reveal that post-systolic slowing of the auricles is a characteristic feature of the arrhythmia and that the degree of slowing is essentially a function of the point of incidence of the initial ventricular deflection.

In the light of the knowledge that the tone of the vagus nerves depends, to a significant degree, upon the pressure within the aorta and carotid arteries, these observations have led us to regard the mechanism of auricular irregularity in A-V heart block as a reflex inhibition of the cardiac pacemaker initiated by a pressure rise within the aorta and carotid arteries, incident to the systolic injection of these vessels.

Observations on the auricular arrhythmia under the influence of atropine and observations on the relative inhibitory effects of normal and premature ventricular systoles in the same subject support this view. Seeming inconsistencies in auricular response to ventricular systole in A-V heart block are discussed in the light of the properties of a reflex vagus mechanism.

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EMBOLISM AT BIFURCATION OF AORTA

Review of Literature and Report of First Case Surviving After Gangrene

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THROMBOSIS of the abdominal aorta was first described by Graham[1] in 1814. In 1898, when Welch[2] reviewed the literature, fifty-nine cases had been collected. Hesse[3] in 1921 collected seventy-three cases. These included forty-one of the cases mentioned by Welch. Wylde,[4] in 1922, reported two cases and, including his own, collected ninety-four cases. From 1922 to 1928, the following cases were reported: Aubertin,[5] two cases; Huesman,[6] one case; Lundblad,[7] two cases; Turreti and Guder,[8] one case; Somalo,[9] one case; Danisch,[10] one case; Menasci,[11] one case; and Tschervakoff,[12] one case. These cases were mentioned in the summary of the literature by Banowitch and Irâ[13] in 1928 when they added five cases which they observed at Long Island College Hospital. In 1935 Rothstein[14] collected and reviewed briefly reports of thirteen cases of thrombosis and embolism of the abdominal aorta which occurred in infants and in children under 15 years of age. To these he added his own case. In the seven-year period following Rothstein's report, thirty-eight cases were recorded in the literature. In 1943 Greenfeld[15] reported five cases. When Santemma,[16] in 1946, reported two cases of aortic occlusion and theorized on the production of signs and symptoms, a summation of eight more cases had been added to the literature by individual case reports. Up to the present time, a total of 174 cases has been reported.

Another case of embolus at the bifurcation of the aorta is herewith presented because of its clinical variation from those already reported.

CASE REPORT

Mrs. A. P., Case No. 32363, a 47-year-old white woman, was admitted to Research Hospital on Jan. 22, 1947, fourteen days after an embolic episode. Approximately fourteen days before admission, there was a sudden attack of pain in the right chest, which was followed by expectoration of bright red sputum and fever. On the next day, the patient had sharp pain below left costal arch which lasted for six hours. Two days later, a sudden excruciating pain was experienced in both legs simultaneously. This pain was associated with tingling and numbness. Color change began soon after this painful episode, and the legs were described as being blue and cold. The degree of change progressed until the lower portion of the legs was black.

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Physical Examination.—The temperature was 101° F.; pulse rate, about 72 per minute and irregular; respirations, 32; and blood pressure, approximately 98/60. No murmurs were audible at this time, and the cardiac sounds were of poor quality and distant. There was a total irregularity of heart rhythm with an apical rate of about 120 beats per minute, making a peripheral pulse deficit of approximately 50. Jugular vessels pulsated and were markedly engorged. The liver was palpable 2.0 cm. below the costal margin, and the spleen was tender.

Fig. 1.—Extremities of Mrs. A. P., fourteen days after onset of gangrene from riding embolus.

The extremities presented the most dramatic findings. A symmetrical pattern of dry gangrene was present over the feet and legs, extending up to 17 cm. below the knees. Gangrene had destroyed the normal contours of the feet and digits to such a degree that the exact outline of the underlying bony framework was apparent through the overlying skin which was dry and black and drawn at the interphalangeal joint spaces. Necrosis extended up the leg, destroying tissue substance (Fig. 1). A hyperemic border of several millimeters surrounded the gan-

grenous area. The skin proximal to this area was of a normal appearance, and sensory modalities were intact. There was a slight degree of edema present which was demonstrated by pitting of the skin. Femoral pulsations were only faintly palpable, while the popliteal arteries could not be felt.

Laboratory Data.—The white blood cells were 19,600. Electrocardiographic tracing showed auricular fibrillation. A 2-meter roentgenogram of the chest at the time of admission revealed clear lung fields. There was, however, gross enlargement of the cardiac shadow in all its diameters, particularly the transverse, and a definite bulge along the middle third of the left heart border.

Diagnosis.—Our diagnosis was: (1) Rheumatic fever (inactive); (2) mitral stenosis; (3) hypertrophy of cardiac chambers (left and right auricles and right ventricle); (4) cardiac insufficiency (left and right ventricular); (5) auricular fibrillation; (6) functional capacity, Class IV (Classification E of American Heart Association classification). Additional diagnoses included: (1) Bilateral gangrene of feet, ankles, and lower halves of legs caused by a saddle embolus at bifurcation of aorta resulting from embolization from the left auricle; (2) recent pulmonary and splenic infarctions due to emboli from right and left auricles, respectively.

Clinical Course.—Several hours after admission, the patient began to chill. Chilling was severe and associated with generalized myoclonic movements. It was felt at this time that absorption of toxins from the necrotic tissue was the cause of this episode, and it was apparent that immediate action was necessary. Because of the cardiac status of the patient (there now were congestive râles in both lung bases), refrigeration was considered to be the treatment for prevention of further absorption of necrotic toxins as well as the best anesthetic in providing for the inevitable amputations. In addition, refrigeration would produce analgesia, obviating the necessity of repeated injections of opiates to relieve pain.

Ice was then placed about both extremities to the level of anticipated site of amputation. Use of ice produced a rapid "physiologic amputation" which allowed time for digitalizing the patient and for improvement in her general condition in preparation for surgical amputation.

Other than refrigeration, sedation was all that was necessary for sufficient anesthesia during surgical procedure. Both gangrenous extremities were amputated above the knees simultaneously by two surgical teams.* Rapid technique was considered essential in preventing shock.

Immediately postoperatively, penicillin and Dicumarol were started. There were no signs of shock, and the course was uneventful with penicillin and Dicumarol being discontinued on the seventh and fourteenth days, respectively. A transfusion of 500 c.c. of citrated bank blood restored the previously low cell count and hemoglobin to a normal level. At the time this paper is written, it has been four months since the patient left the hospital, and the stumps are healed. The patient carries on some of her household duties in a wheel chair. Orthopedic surgeons* are conditioning the stumps for artificial limbs in two months.

DISCUSSION

Cardiac thrombi which may cause aortic embolism are of two types: the smaller type, which arises from mycotic vegetations, usually on the mitral or aortic valves, associated with valvular endocarditis; and the larger type that is usually found where circulation is slowest, as in the auricular appendages and in the apices of the ventricles between the columnae carneae. Most frequent sources of arterial emboli in the systemic circulation are mural thrombi in the left auricle or left ventricle. These form in a fibrillating left auricle present in rheumatic or arteriosclerotic heart disease. In mitral stenosis, mural thrombi from an enlarged left auricle, especially when fibrillating, may send an embolus to lodge at the aortic bifurcation. In myocardial infarction having subendo-

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cardial localization in the left ventricle, mural thrombi form and some may break loose to become arterial emboli. Mural thrombi also form in an enlarged left ventricle in cases of congestive failure resulting from hypertension or from coronary artery disease.

The portion of the abdominal aorta usually affected by an embolus is that below the origin of the mesenteric arteries. There are two types of emboli responsible for the syndrome of riding embolus, one of which completely occludes the lower end of the aorta and the other only incompletely occludes it. When either type of these emboli strikes the aortic bifurcation, terrific reflex angiospasm occurs instantly throughout the entire arterial system of both legs. In many instances, immediate occlusion of the lower end of the aorta results from intense localized spasm. Distal, soft, taillike secondary propagation thrombus formation starts in several hours and extends a variable distance into the iliac arteries. The farther the secondary thrombus formation extends down the iliacs and the longer the delay in treatment, the more collateral arteries are occluded. Secondary propagation thrombi usually extend farther down one iliac artery than down the other, so that variations in symptoms, prognosis, and treatment follow.

In the majority of the cases reported in the literature, the onset of symptoms has been acute. The patient is suddenly seized with a severe, sharp, intense, agonizing pain, referable in most instances to the lower extremities. Intense pain may not necessarily be present at the start, and in nearly half the cases numbness or paralysis points to a sudden occlusive arterial lesion. Tenderness or pain over distal propagation plugs occurs late. Backache is a special symptom to localize the lesion to the aortic bifurcation. Skin changes include pallor or mottled cyanosis, coldness of entire lower extremities below the level of adequate collaterals, collapsed veins, loss of sensation, diminished reflexes, and evidence of partial paralysis of one or both extremities.

Thus, this dramatic picture presents varied symptoms and signs, but early diagnosis and prompt treatment are possible if physicians think of this syndrome in types of heart disease mentioned and examine peripheral arterial pulsations routinely in such patients when making rounds.

Differential Diagnosis.—Sudden arterial occlusion of one extremity has been mistaken for embolism at the bifurcation of the aorta, but findings are always unilateral. Likewise, the clinician must be cognizant of the difference between single arterial occlusion with or without gangrene and saddle embolus with or without gangrene in which the propagation thrombus involves just one iliac artery. Here again findings are always unilateral in single arterial occlusive lesions, while in saddle embolus there are findings of coldness, pallor, and numbness in both extremities from the onset. Should gangrene later develop in one leg, confusion should not ensue because the other leg will not show any change from normal in a single arterial occlusive lesion but will exhibit findings in the case due to saddle embolus. A patient with venous obstruction has an extremity with normal or elevated skin temperature, distended veins, cyanosis, edema, and in which arterial pulsations can frequently be identified. Gangrene seen in the

patient with arteriosclerosis obliterans as a result of intravascular thrombosis is easily differentiated from the sudden and dramatic syndrome under discussion. Functional peripheral circulatory disturbances or thromboangiitis obliterans with its arterial insufficiency of the upper extremities also are not likely to be confused.

Treatment.—Treatment of saddle embolus is the same as that for sudden, single, peripheral arterial occlusion in general with special attention given to several points which apply to this entity specifically. Prophylactically, prevention is possible if Dicumarol is administered routinely in coronary occlusion when such patients are in a hospital where accurate determination of prothrombin time can be performed and there are no contraindications.

The principles for treatment of sudden arterial occlusion, as laid down by Allen, Barker, and Hines, Jr.,[17] are followed in the early stage which is the pregangrenous stage. There are three things *not* to do in these cases. First, do not elevate the extremities; second, do not apply heat; and third, do not delay treatment. An opiate is given as soon as the diagnosis is made; morphine sulfate, grain ¼ to ½, is administered, giving part of the solution intravenously and the balance subcutaneously. Then, papaverine hydrochloride is given intravenously in doses of 1 to 2 grains every four hours. The first dose may be injected into a femoral artery. This is to relax arterial spasm, which is further relieved by maintaining temperature of the room between 85° and 95° Fahrenheit. An ounce or two of whiskey is, in most instances, the best sedative as well as being a vasodilator. The patient should be placed on an oscillating bed. Heparin and Dicumarol are started as early as possible in all cases.

Failure to gain restoration of adequate circulation in a few hours calls for procaine sympathetic block. Should the circulation not be restored in about eight to twelve hours after onset of the embolic phenomenon and the carrying out of procedures described herein, embolectomy is performed under local or regional anesthesia. Since anticoagulant therapy has been used widely, circulation is restored more often and embolectomy required fewer times than formerly.

When gangrene is already present, bilateral amputation is the only course, anticoagulants being of no help at this late stage. Management of this late stage, which is the gangrenous stage, is presented so that life, not limbs, may be saved. Cardiac reserve must be evaluated and proper measures taken to restore it if necessary. Inadequate digitalization, if noted by signs of cardiac insufficiency, can be overcome carefully yet quickly with glycosides of digitalis since there may not be time enough to wait for the slow effects of whole leaf.

Physiologic amputation is performed quickly by placing the legs in ice to within four inches of the anticipated site of amputation. Place a tourniquet at this level. This treatment can be kept up for several days, if necessary, to get the patient into best possible shape for surgery. Four hours before surgery, apply ice at least four inches above amputation site, and apply the second tourniquet at this level. By this method tissue asphyxiation and a viable stump are obtained. Do not add salt because this produces freezing of tissue and results in necrosis of stump, necessitating secondary amputation.

Most often amputation below the knee is satisfactory in embolus at the bifurcation of the aorta.[18] Though the site of the embolus is higher, the level of amputation is lower than for most cases of single artery occlusion having the same extent of gangrene. This is because riding embolus occurs more often in middle-aged individuals who, as a rule, will have more general vitality, less arteriosclerosis, and better collateral circulation than elderly patients. As a result of all of these factors, the intima will be less likely to be damaged irreversibly by ischemia from angiospasm, whereas in the elderly patient, more extensive arterial thrombosis and poor collateral circulation will result in amputations being done more frequently above the knees.

Immediately postoperatively, Dicumarol is started to prevent venous thrombosis. This phase of treatment eliminates a common cause of postoperative death from amputation, namely, pulmonary embolism from thrombosis of a leg vein. Refrigeration prevents postoperative shock so that patients with poor cardiac reserve, like those in functional Classes III and IV (American Heart Association), can now survive. The possibility of morbidity or mortality from postoperative infection will usually be prevented by continuing the administration of penicillin for one week.

Prognosis.—The prognosis is always grave. Hesse[3] showed that 95 per cent of seventy-three patients died under conservative therapy. In the review by Rothstein,[14] it was brought out that 112, or 91 per cent, of the 123 patients reported up to 1935 expired. In the summary by Greenfield[15] in 1943, of a total of 161 patients, 147, or 91.3 per cent, succumbed. Death occurred from within several hours to three months after onset of symptoms. Mortality following gangrenous changes has been 100 per cent. The case reported herein falls into a different group, especially since the gangrene had been present for fourteen days prior to surgery. Aside from the duration of gangrene, our patient was, in addition, a very poor surgical risk (Class IV-E) as are all such individuals who have auricular fibrillation and myocardial insufficiency and who experience arterial embolism. As far as a review of the literature shows, this is the only patient to survive after extensive gangrene of such duration.

SUMMARY

1. Attention has been directed to a complete review of the literature concerning embolism at the bifurcation of the aorta.

2. Emboli occluding the abdominal aorta are of cardiac origin.

3. Symptoms of abdominal aortic obstruction may be slowly progressive or rapid in onset.

4. Sudden, single arterial embolic occlusion, arterial thrombosis of one extremity, and venous obstruction are differentiated from riding embolus.

5. Prophylaxis of saddle embolus is discussed, as well as treatment of the early and late stages.

6. A case of embolus at the bifurcation of the aorta is presented because of its clinical variation from those already reported, because refrigeration, utilized

for both therapy and anesthesia, altered a heretofore grave prognosis, and because our patient is the first one reported who survived after gangrene of such duration.

7. Mortality following gangrenous changes has been 100 per cent; but now, with refrigeration for both therapy and anesthesia, with anticoagulants, and with penicillin, these heretofore doomed patients can survive.

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ELECTROCARDIOGRAPHIC CHANGES IN TYPHOID FEVER AND THEIR REVERSIBILITY FOLLOWING NIACIN TREATMENT

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ANY infectious disease may affect the heart and the circulatory system. The cardiac involvement may be so severe as to produce marked clinical manifestations and even heart failure and death. In such cases, pathologic examination reveals profound changes, manifested either by toxic parenchymatous degeneration or by actual myocarditis, that is, inflammatory infiltration of the heart muscle. Chief among the infectious diseases severely affecting the heart are rheumatic fever, diphtheria, and syphilis. The cardiac involvement in these diseases is evidenced by clinical manifestations and by abnormalities in the various phases of the electrocardiogram. In recent years electrocardiographic alterations have been described in various acute infections not directly affecting the heart, such as pneumococcus pneumonia,[1] infectious hepatitis,[2] mumps,[3] and infectious mononucleosis.[4] These electrocardiographic changes are transient and disappear after recovery.

Of the infectious diseases rarely affecting the heart anatomically, typhoid fever has been the subject of a number of electrocardiographic studies. Most of these investigations were reported in the European literature. Clerc and Levy[5] examined the electrocardiograms of ten cases of typhoid fever, in five of which electrocardiographic changes were found. The alterations consisted of diphasic or negative T waves, especially in Lead II. Arieff and Tigi[6] found a high incidence of electrocardiographic alterations in a series of thirty-five cases of typhoid fever. The abnormalities consisted of prolongation of the P-R interval in eighteen cases and flattening of the T waves in the remaining seventeen cases. According to these authors the changes usually appear during the acme, and occasionally, one to two weeks after defervescence. Chagas[7] described electrocardiographic changes in six cases of typhoid fever. In two of them, disturbances in the rhythm were found, in one there was total, and later partial, auriculoventricular block, and in the three remaining cases T-wave changes were noted. Bucham and Daniels[8] observed changes of the T waves, which were negative, flat, diphasic, or isoelectric in five out of nineteen cases of typhoid and paratyphoid fever. No data were recorded regarding the duration of the T-wave abnormalities. Lukomski[9] observed the following changes in a series of sixty cases of typhoid fever: prolonga-

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tion of the P-R interval in 33 per cent and S-T and T-wave abnormalities in about 30 per cent, but this also included cases with negative T waves in Lead III only. The T-wave changes generally appeared at the height of the temperature and persisted after defervescence, disappearing only several weeks after recovery. Gurewitsch[10] examined sixty-five children suffering from typhoid fever. In twenty-four cases pathologic changes in the electrocardiogram were found; these consisted of flattening of all the deflections, especially of the T waves. These changes were sometimes observed even as late as six months after recovery. This author stressed the fact that the severity of the typhoid infection bore no relationship to the presence of electrocardiographic abnormalities. Giraud-Costa and Raybaud[11] recently summarized their electrocardiographic findings in 510 cases of typhoid fever studied since 1933. The most frequent changes in the electrocardiogram were alterations of the T waves, which were flat, diphasic, or inverted. Prolongation of the P-R interval was also observed in a number of cases. Other disturbances in conduction and arrhythmias were rare. The changes in the electrocardiogram appeared at the height of the disease and continued into the convalescent period. According to these authors, the patient enters and leaves the hospital with a normal electrocardiogram.

Reports on this subject in the American literature are scarce. Brow[12] reported electrocardiographic findings in sixty-five cases of typhoid fever, in 21.5 per cent of which prolongation of the P-R interval was found. Only two cases showed T-wave changes. The earliest change appeared on the second day, and the latest on the forty-third day. No clinical signs of cardiac involvement were present in the entire group. Porter and Bloom[13] examined thirty cases of typhoid fever, in fourteen of which significant changes in the electrocardiogram appeared between the ninth and the forty-fourth day. In nine of these cases, prolongation of the P-R interval was observed, while alterations of the T waves were seen in only four cases. These changes lasted longer than six days in only two instances. From a clinical point of view there were no abnormal manifestations of the cardiovascular system. Stuart and Pullen,[14] in a recent clinical study of 360 cases of typhoid fever in New Orleans, found one case with prolongation of the P-R interval and five cases with T-wave changes among sixteen cases examined electrocardiographically.

Our observations are based upon electrocardiographic studies on fifty cases of typhoid fever treated during the past three years. With a single exception, all were without clinical evidence of previous heart disease. There were no fatalities in this series of cases; in the majority the course was of moderate severity. No serious complications were encountered except for intestinal hemorrhage in two cases, and agranulocytosis in one. Fifteen cases in which repeated chills, a high degree of toxemia, or continued diarrhea appeared during the course of the disease received sulfa drugs or penicillin as long as these manifestations lasted. Otherwise, small doses of antipyretics and sedatives were prescribed. The diet during the febrile period consisted of 240 Gm. of carbohydrates, 90 Gm. of fat, and 75 Gm. of proteins given in liquid or semiliquid form. Serial electrocardiographic examinations were made upon admission to the hospital and at frequent intervals during the course of the disease and the convalescent period. Standard limb leads

and precordial Lead IVF were recorded. Each recording was made with the patient in the recumbent position. In addition, the routine cardiovascular examinations were performed, special attention being paid to the appearance of heart murmurs and myocardial insufficiency.

RESULTS

Among the total of fifty cases, fifteen showed no electrocardiographic changes on repeated examinations during the entire period of observation. This group included four cases in which the typhoid infection was severe. The average duration of the febrile period in this group was twenty-six and one-half days. Electrocardiographic alterations were found in a group of thirty-five cases with an average febrile period of twenty-eight days. The age incidence in this group did not differ significantly from that of the other group with abnormal electrocardiographic findings. A description of these changes follows.

P-R Interval.—Only three cases showed a prolonged P-R interval (0.24, 0.25, and 0.28 second, respectively). These changes appeared during the febrile period. In one case the P-R interval remained prolonged for only six days and became normal while fever was still present. In the other two cases the prolonged P-R interval persisted into convalescence.

P Wave.—P waves showed no significant deviations from the normal.

QRS Complex.—In two cases there was a decrease in the voltage of the QRS complex during the febrile period. The voltage returned to normal during convalescence.

Q-T Interval.—This was calculated by Bazett's formula: $QT = K\sqrt{R\text{-}R}$, where K is a constant. The average value for K in normal men is 0.374, and in normal women, 0.383.[15] There was no significant deviation from these values during the disease or after recovery.

RS-T Segment.—Changes in the RS-T segment were not significant. In only four cases was there a deviation of 1.0 mm. or less from the base line.

T Wave.—The most conspicuous changes were found in the T waves. All thirty-five cases showed some degree of abnormality in the T waves, which were of low amplitude (less than 2.0 mm.), isoelectric, or diphasic. The following (Table I) gives an account of the frequency of T-wave changes in various leads.

TABLE I.

T-wave changes in all leads	24
T-wave changes in Leads I, II, and IVF	1
T-wave changes in Leads II. III, and IVF	2
T-wave changes in Leads I and IVF	2
T-wave changes in Leads I and II	4
T-wave changes in either Lead I or Lead II	2
Total	35

The course of the T-wave alterations was followed throughout the disease. As soon as the T waves became flatter, electrocardiograms were taken frequently to record the successive changes. The abnormalties of the T waves appeared in twenty-eight cases after defervescence, in two cases during the febrile period, and in the remaining five cases in the decrescent phase of the febrile period. There was no relationship between the severity of the disease and the degree of the electrocardiographic abnormalities, nor did the duration of the disease or the presence of complications have any apparent bearing on the severity of the electrocardiographic alterations. No clinical cardiovascular disturbances or subjective complaints referable to the heart were noted in the patients showing marked electrocardiographic changes.

THE EFFECT OF NIACIN UPON THE ELECTROCARDIOGRAPHIC CHANGES

Since in the majority of patients the T-wave alterations appeared simultaneously with clinical signs of vitamin B deficiency and since the electrocardiographic changes resembled those seen by us in niacin deficiency,[16] twenty-three patients were given niacin. Daily doses of 300 to 600 mg. of niacin were given orally and in some cases also intravenously. This treatment was begun after the electrocardiographic alterations had become pronounced and constant. In all

TABLE II. ELECTROCARDIOGRAPHIC FINDINGS

CASE NO.	SEX	AGE	BEFORE TREATMENT	AFTER TREATMENT WITH NIACIN
1	M	35	T_1, T_4 flat,* T_2, T_3 isoel. S-T_2, S-T_3 depressed	T_1++, T_2+++, T_4+++ S-T_3 isoel.
2	M	17	T_1, T_4 flat, T_2 isoel.	T_1++, T_2++, T_4+++
3	M	16	T_1, T_2, T_4 flat	T_1++, T_2++, T_4+++
4	F	47	T_1, T_2 flat	T_1++, T_2+
5	F	18	T_1, T_2, T_4 flat S-T_1 depressed	T_1++, T_2+, T_4++ S-T_1 isoel.
6	F	47	T_1, T_4 diphas., T_2, T_3 isoel.	T_1++, T_2+, T_4++
7	F	31	T_1, T_2, T_4 flat	T_1++, T_2+, T_4++
8	F	30	T_1, T_4 flat, T_2 isoel.	T_1++, T_2++, T_4++
9	F	45	T_1 flat, T_2, T_4 isoel.	T_1++, T_2++, T_4++
10	F	25	T_1 flat, T_2, T_3, T_4 isoel.	T_1+++, T_2++, T_4+++
11	M	24	Low voltage of QRS T_1, T_4 flat	 T_1++, T_4+++
12	M	25	T_1, T_2, T_3, T_4 isoel.	T_1++, T_2++, T_4+++
13	F	24	T_1, T_2, T_4 flat	T_1++, T_2+, T_4+++
14	F	29	T_1, T_2 flat, T_4 isoel.	T_1+, T_2+
15	M	19	T_1, T_2, T_3 flat S-T_2, S-T_3 depressed	T_1++, T_2++ S-T_2, S-T_3 isoel.
16	F	42	Low voltage of QRS T_1, T_2 flat, T_4 isoel.	 T_1++, T_2++
17	M	30	T_1 isoel., T_2, T_3, T_4 flat	T_1+, T_2++, T_3+, T_4+++
18	F	28	T_1, T_4 flat, T_3 isoel.	T_1+, T_2++, T_4++
19	M	32	T_1, T_2, T_4 flat	T_1+, T_2+, T_4++
20	M	32	T_1, T_3 isoel., T_2, T_3 flat	T_1+, T_2++, T_3+
21	F	32	T_1, T_4 isoel., T_3 isoel.	T_1+, T_2+, T_3+
22	M	45	T_1, T_2, T_3 flat, T_4 isoel.	T_1+++, T_2+++, T_4++
23	M	23	T_1, T_2, T_4 flat	T_1++, T_2+++, T_4+++

*The term "flat" is used to signify a voltage of less than 2 millimeters.

cases there was marked improvement in the electrocardiogram following this treatment. The return of the electrocardiogram to normal was observed after short periods of niacin medication: in six cases, after two days; in twelve cases, after three to five days; and in four cases, after six to ten days. Table II presents the electrocardiographic findings before and after treatment. The degree of elevation of the T waves was designated as Plus 1 (+), corresponding to an elevation of 0.5 mm. +0.25 mm.; as Plus 2 (++), corresponding to an elevation of 1.0 mm. +0.25 mm.; and as Plus 3 (+++), corresponding to an elevation of 1.5 mm. and more.

The following case histories illustrate the development of the electrocardiographic changes in typhoid fever and the effect of niacin treatment on these changes.

CASE 1.—R. E., a 30-year-old woman, was admitted on Nov. 1, 1945, with a history of general malaise, headache, anorexia, and fever of a fortnight's duration. The fever started with a chill which was followed by a sudden rise of temperature to 41° centigrade. The pyrexia persisted, ranging between 38° C. in the morning and 41° C. in the evening.

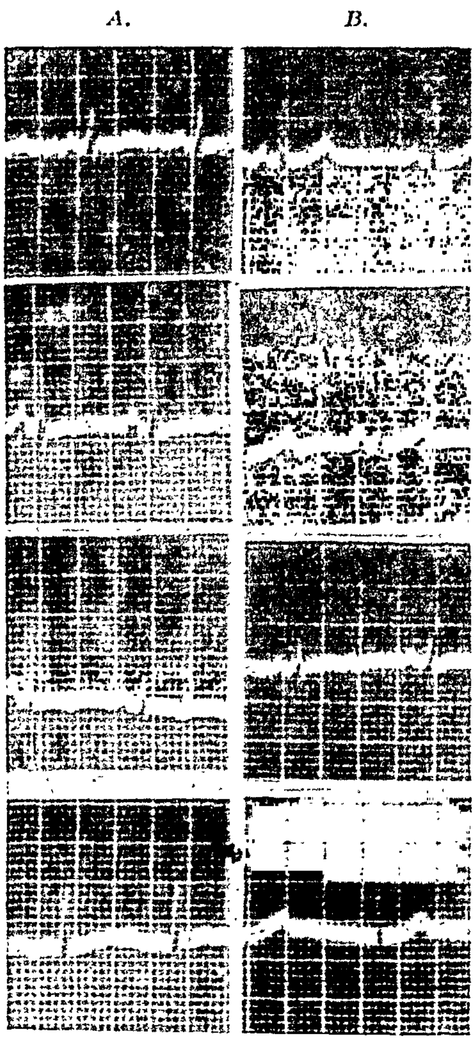

Fig. 1.—*A*, Electrocardiogram taken during convalescence: T_1, T_2 isoelectric, T_4 diphasic. *B*, After two days' treatment with niacin, the electrocardiogram is normal.

On admission, the patient appeared severely ill, the tongue was coated, and the spleen was palpable 2.0 cm. below the left costal margin. Neurological examination revealed rigidity of the neck, a hyperactive right patellar reflex, and increased skin sensitivity to pain in both legs. The Kernig sign was negative. The white blood cells were 5,000, with 56 per cent neutrophiles, 30 per cent lymphocytes, 6 per cent monocytes, and 8 per cent band-form neutrophiles. Cerebrospinal fluid after lumbar puncture gave a positive Pandy reaction and a normal cell count. Eight days after admission rose spots were seen, and the Widal agglutination test, which had been negative on admission, became positive.

On November 16, thirty-one days after the onset of the disease, the temperature became normal and the patient made an uneventful recovery. During the convalescent period she complained of a burning sensation in the tongue which was bright red and showed atrophy of the papillae.

Serial electrocardiograms were made during the patient's stay in the hospital. Three normal tracings were recorded during the febrile period. After the fall in temperature, the T wave became flat and the electrocardiogram became definitely abnormal. Two electrocardiograms on November 20 and November 25 showed the same alterations: T_1 and T_2 isoelectric, T_3 inverted, and T_4 diphasic (Fig. 1,*A*). On November 25, treatment with niacin, 600 mg. daily, was commenced. After two days of treatment, a marked elevation of the T waves was noted and the record became normal (Fig. 1,*B*).

Niacin excretion in the urine during the course of the disease was examined in this case. A continuous and gradual decrease was observed; from 5.5 mg. per liter at the height of the

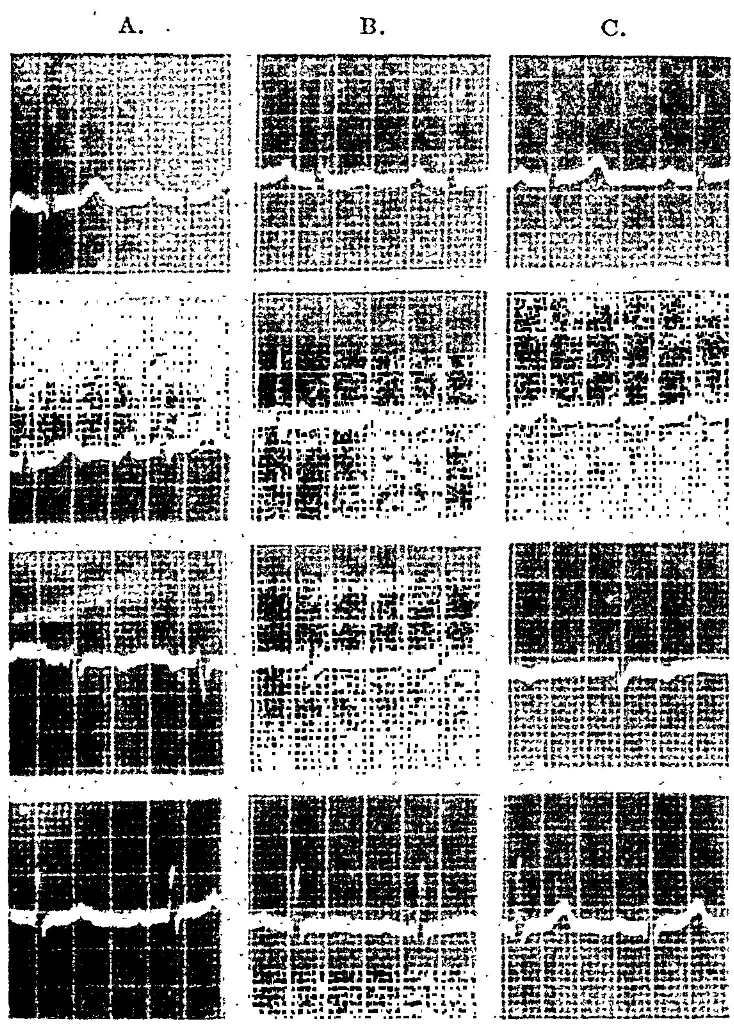

Fig. 2.—*A*, Normal electrocardiogram taken during the febrile period. *B*, Electrocardiogram taken after defervescence: T_1 flat, T_2, T_3, and T_4 isoelectric. *C*, After two days of treatment with niacin the tracing became normal.

disease to 0.60 mg. per liter at the time of convalescence. The lowest values of niacin were obtained at a time when electrocardiographic alterations were most pronounced.

CASE 2.—T. S., a 25-year-old woman, was admitted on Sept. 4, 1945, complaining of fever of a fortnight's duration. The disease had started with anorexia, malaise, headache, and backache, the temperature rising gradually to 39° centigrade. On admission, a coated tongue, relative bradycardia, splenomegaly, and a rose-colored rash were found. The number of leucocytes was 6,500, with 60 per cent neutrophiles, 31 per cent lymphocytes, and 6 per cent band-form neutrophiles. Widal agglutination test was positive. The fever continued for another fortnight, after which the patient gradually recovered. During the febrile period, two electrocardiograms were taken which were both normal (Fig. 2,*A*). During convalescence two electrocardiograms, taken at an interval of five days, showed identical changes: T_1 flat and T_2 and T_4 isoelectric (Fig. 2,*B*). On September 24, treatment with 500 mg. of niacin daily was started. After two days of treatment the T waves in Leads I, II, and IV showed a marked increase in voltage (Fig. 2,*C*). The electrocardiogram became normal and similar to that observed on admission.

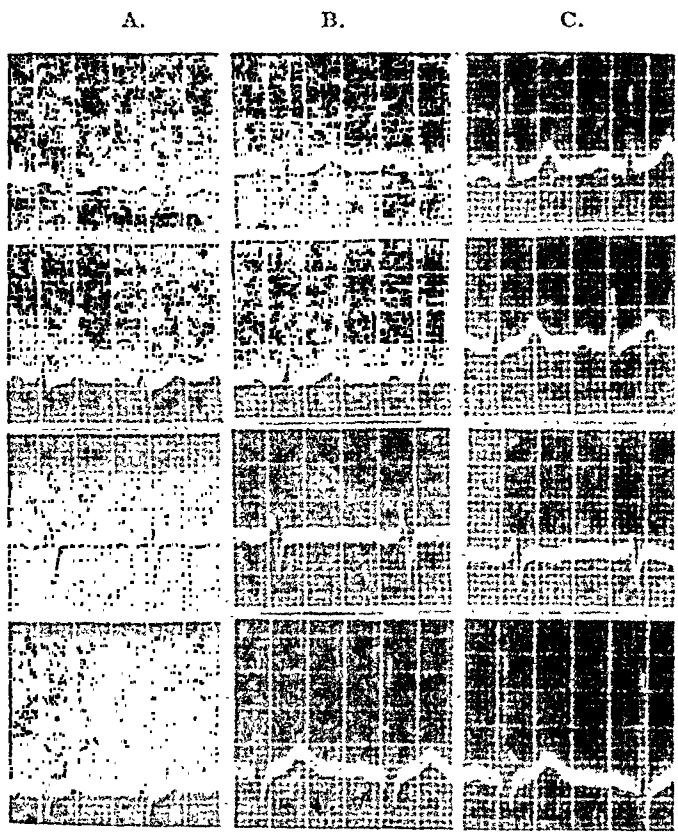

Fig. 3.—*A*, Electrocardiogram taken at the time of defervescence: flat T waves in all leads. *B*, After two days of niacin administration, increase in the voltage of T waves. *C*, Further elevation of the T waves after additional treatment of three days.

CASE 3.—R. L., a man, 45 years of age, was admitted on July 25, 1944, complaining of headache, anorexia, malaise, and fever which had started eight days prior to admission. During this period the temperature rose gradually to 39° centigrade. On admission, the patient was somnolent and showed bradycardia, splenomegaly, and a rose-colored rash on the abdomen. The number of leucocytes was 5,600, with 56 per cent neutrophiles, 40 per cent lymphocytes, and 4 per cent band-form neutrophiles. Eight days after admission, the Widal agglutination test was positive and typhoid bacilli were cultured from the bone marrow. The course of the disease was severe and sulfonamides were administered because of increasing toxemia. Intestinal bleeding occurred three weeks after admission, and two blood transfusions were given.

Five weeks after admission the temperature began to fall and gradually returned to normal within a fortnight. During defervescence, the patient complained of a burning sensation in the tongue; on examination the papillae were found to be atrophic and the color of the tongue was fiery red.

Two electrocardiograms were recorded during the febrile period, both of which were normal. At the time of defervescence, the T waves became flat in all leads (Fig. 3,*A*). Treatment with niacin, 500 mg. daily, was begun on September 5. After two days of niacin administration there was an increase in the voltage of the T wave in Leads I, II, and IV (Fig. 3,*B*). After three more days of treatment, further elevation of the T waves was observed (Fig. 3,*C*).

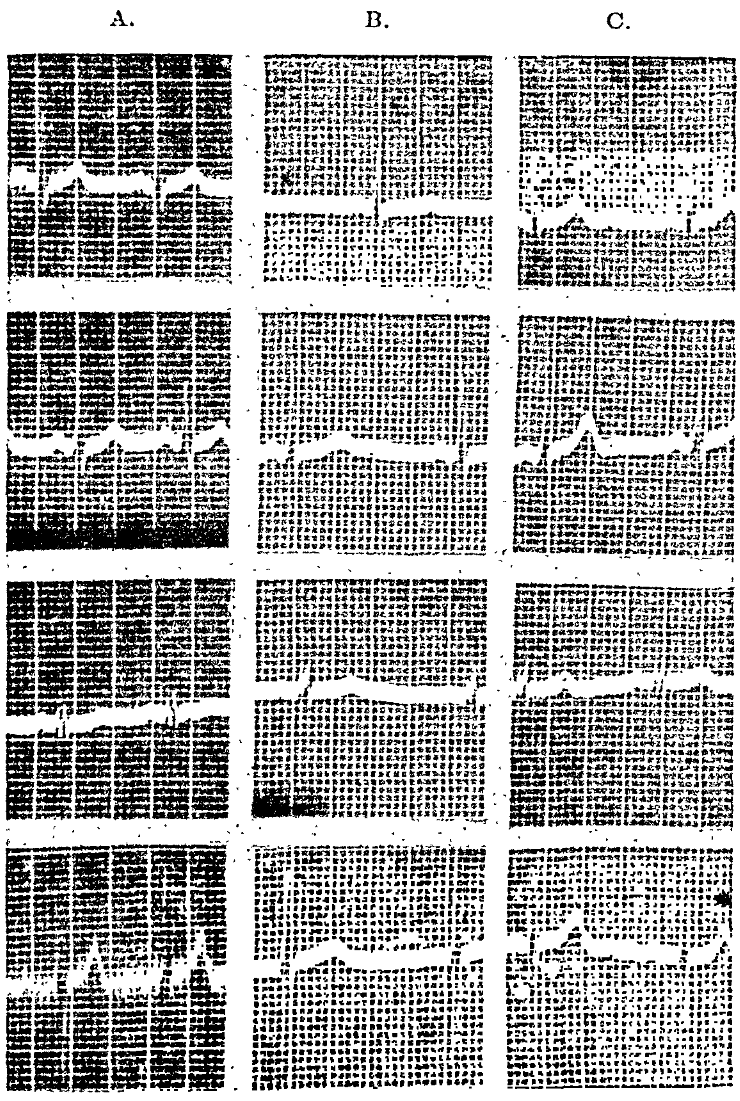

Fig. 4.—*A*, Normal electrocardiogram taken during the febrile period. *B*, Electrocardiogram taken during convalescence: T_1 almost isoelectric and T_2 and T_4 reduced. *C*, After three days' treatment with niacin, marked elevation of all T waves.

CASE 4.—N. B., a man, 23 years of age, was admitted on July 23, 1947, complaining of headache, malaise, and fever which had started three days earlier. On admission, the patient was in a state of somnolence; the main findings were bradycardia, splenomegaly and a coated tongue. The leucocyte count was 9,200, with 66 per cent neutrophiles, 17 per cent lymphocytes, 4 per cent monocytes and 13 per cent band-form neutrophiles. Widal agglutination test was positive. The fever rose gradually to 40° centigrade. The patient complained of severe headache, and five days after admission, there was a marked rigidity of the neck with positive Kernig sign. A lumbar puncture was performed but no pathologic findings were present in the cerebro-

spinal fluid. On the same day, treatment with penicillin, 200,000 units daily, was begun. The treatment was continued for one week, at the end of which period the temperature dropped to normal. The patient made an uneventful recovery.

A series of electrocardiograms was made during his stay in the hospital. On July 27, at the height of pyrexia, a normal electrocardiogram was obtained (Fig. 4,*A*). After the decline of the temperature, the T waves became flat and the electrocardiogram was definitely abnormal. In the period from August 2 to August 15, five records were taken, all of which showed similar alterations. Fig. 4,*B* shows the electrocardiogram taken on August 15: T_1 was almost isoelectric and T_2 and T_4 were flat. On the same day, treatment with niacin, 600 mg. daily, was started. After three days of this treatment a marked elevation of the T waves was noted and the record became normal (Fig. 4,*C*).

In twelve cases showing T-wave changes niacin was withheld, in order to follow the spontaneous regression of these alterations. In all but two of these cases a gradual improvement of the electrocardiographic pattern during the convalescent period could be observed. In this group, an average of twelve and one-half days was required for the restoration of the electrocardiogram to normal. In one patient, electrocardiographic abnormalities were still present twenty-six days after the fall of temperature, and follow-up was not possible. In the second patient, in whom the typhoid infection was severe and complicated by massive intestinal hemorrhages, the T waves became flat thirty days after the onset of the illness while the temperature was subfebrile. These changes were still present on his discharge eighteen days later and could not be further observed.

DISCUSSION

Our observations, as well as others reported in the literature, clearly demonstrate that electrocardiographic changes are of frequent occurrence in typhoid fever. Myocarditis due to the typhoid infection must be considered first among possible causes for these electrocardiographic findings. The assumption that myocarditis is responsible for the electrocardiographic changes in all cases appears improbable for the following reasons. There was a high frequency (70 per cent) of electrocardiographic abnormalities in our material, and it is unlikely that myocarditis was present in such a high percentage of cases. Pathologic studies in typhoid fever indicate that myocarditis is rare in this disease.[17] Slight to moderate toxic changes may be found in the heart muscle and interstitial tissue in patients dying of typhoid fever. The anatomic changes consist of cloudy swelling and infiltration with small round cells. Such findings are hardly to be expected in mild or moderate cases of typhoid fever.

The absence of clinical manifestations of cardiovascular involvement and the lack of parallelism between the severity of the disease and the presence and degree of electrocardiographic alterations cast further doubt on the assumption that myocarditis is the underlying cause of the cardiographic abnormalities. It appears, therefore, that the cause of the electrocardiographic alterations, should be sought rather in noninflammatory myocardial changes.

The change in the electrocardiographic pattern, which concerns mainly the final deflection of the ventricular complex, is frequently seen in metabolic disorders, such as alkalosis,[18] diabetic acidosis,[19] and vitamin B deficiency.[20] The

tact that the electrocardiographic alterations in our cases appeared during convalescence at a time when clinical manifestations of vitamin deficiency frequently appeared, as well as the absence of clinical signs of cardiac involvement, led to the assumption that the underlying cause of the electrocardiographic abnormalities was a metabolic disturbance in the heart muscle due to vitamin deficiency. The similarity of these changes to those seen in niacin deficiency justified the therapeutic trial of niacin. The effect of the administration of niacin was marked in all instances, and the electrocardiograms returned to normal after very short periods of treatment. In some cases striking improvement was observed after only two to three days of niacin administration. Thus, the response to niacin in patients with typhoid fever was similar to that in patients suffering from pellagra, and it is reasonable to suppose that the electrocardiographic changes in typhoid fever, as in pellagra, are due to niacin deficiency.

The rate of niacin excretion was examined during the course of the disease in nineteen cases. A uniform and gradual decrease of niacin excretion took place in all cases, the lowest excretion of niacin being found during convalescence. This decrease was explained by one of us (K.B.) as being due to increased requirements, disturbed intestinal synthesis and absorption, and the frequently low food intake during the course of the disease.[21] A definite relationship was observed between the level of niacin excretion and the electrocardiographic changes, the latter appearing at the time when the niacin excretion was at its lowest. The spontaneous improvement in the electrocardiogram in those cases which were not treated with niacin may be explained by the increased niacin content of the food during convalescence, the reduced requirements, and the improved absorption. This was indeed seen in four of these cases in which a spontaneous rise in the amount of niacin in the urine occurred late in convalescence.

It must, however, be borne in mind that deficiences may be multiple and that a lack of various components of the vitamin B complex may occur simultaneously. Peripheral neuritis, as seen in thiamine deficiency, was present in six of our cases. In fifteen cases the amount of pyruvic acid in the urine was also found to be markedly increased during the convalescent period. This finding also points to thiamine deficiency. Since the described electrocardiographic changes are not specific for niacin deficiency, they might also be caused by thiamine deficiency. The prompt therapeutic response to niacin treatment, however, supports the contention that the cause of the electrocardiographic changes is a deficiency of niacin.

SUMMARY

Serial electrocardiographic examinations were made in fifty cases of typhoid fever. In thirty-five cases, deviations from the normal were observed. The alterations were mainly present in the T waves, which became flat, isoelectric, or diphasic, usually after defervescence. Twenty-three patients with T-wave changes were given niacin which resulted in rapid normalization of the electrocardiogram. In twelve cases with pathologic electrocardiograms, a spontaneous gradual return to normal was observed.

The rapid effect of niacin and the development of the electrocardiographic changes concomitant with reduced niacin excretion in the urine is considered as evidence that the described electrocardiographic abnormalities are due to niacin deficiency.

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Clinical Reports

BILATERAL NONTRAUMATIC ILIOFEMORAL THROMBOPHLEBITIS IN A CHILD

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ILIOFEMORAL thrombophlebitis, though commonly seen in adults, is rare in children. In a series of 254 cases of thrombophlebitis of the iliofemoral vein reported by Allen, Barker, and Hines,[1,2] the youngest patient was 10 years of age. The following case is an example of nontraumatic iliofemoral thrombophlebitis in a 6-year-old child. The onset followed an ill-defined respiratory and gastrointestinal infection.

N. D., a 6-year-old school boy with essentially normal family, past, and birth histories, had a mild upper respiratory infection early in May, 1947. This was characterized by a moderate fever, swelling of the glands of the left cervical region, general malaise, and followed by a brief attack of diarrhea. During the acute episode a diagnosis of "mumps" was made by the family physician. The correctness of this diagnosis was in doubt. The patient apparently recovered from this acute illness after a period of about ten days and returned to school. Several days later he had some pain in the region of the left buttock, associated with slight fever and inability to walk or sit down on that side. Within forty-eight hours pain and fever had subsided and the patient was up and about for two days. On the third day the child developed fever, diarrhea, and abdominal pain. At that time a diagnosis of "intestinal grippe" was made. After a few days of bed rest the diarrhea subsided and then the patient began to develop pain in the left thigh and leg. Examination on May 18, 1947, revealed an acutely ill child with a swollen left lower extremity. The swelling extended from the inguinal ligament to the tips of the toes. The left iliac pulse was barely palpable. It was the most distal palpable pulse in the left lower extremity. The left great toe was 4° F. (2.2° C.) cooler than the right by skin thermocouple test. The right iliac pulse was easily palpated. The right popliteal pulse could be palpated but the anterior and posterior tibial pulses on the right side were not palpable.

On May 19, 1947, the left iliac pulse could not be felt. The left foot assumed a slate blue cyanosis and was 10° F. (5.5° C.) cooler than the right when tested with a skin thermocouple on the plantar aspect of the great toes. A left paravertebral block was performed at the levels of the second, third, and fourth lumbar sympathetic ganglia. Patient was initially anesthetized by open drop ether; 3.0 c.c. of 1 per cent procaine was placed into each space and this was followed by 2.5 c.c. of Bromsalizol in oil.[3]

On May 20, 1947, there was marked improvement in the appearance of the left lower extremity; the left foot was only slightly cooler than the right and there was a marked reduction in the tension of the tissues. The temperature had dropped to 100° F. (37.7° C.) and pain was

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completely relieved. The penicillin therapy which had been started on May 18, 1947, 30,000 units every three hours, was continued.

During the next few days the general and local condition continued to improve; but on May 22, 1947, the patient began to develop pain and swelling in the right lower extremity. The right iliofemoral pulse was not palpable and the right leg began to become cold, cyanotic, and painful. A paravertebral block was performed on the right side, using the same technique that was used on the left. An immediate improvement in pain, swelling, and tenderness was noted. By May 31, 1947, the general condition had improved sufficiently for the patient to be up and around with bilateral elastic bandages from instep to the tibial tubercle.

During the interim immediately following the second block, the patient refused to extend his lower extremities and held them flexed toward the abdomen. Edema developed in both feet and, in order to avoid contracture and stasis, Buck's extensions were set up with 3-pound weights for each leg. This was well tolerated by the patient and succeeded in overcoming the persistent flexion at the knee and hip. Patient also developed a mild secondary anemia for which two transfusions, each of 250 c.c. citrated blood, were given.

Fig. 1.—Note prominent veins on abdomen. This photograph was taken twenty days after the onset of acute swelling in the left (initial) lower extremity. Patient was up and around with elastic bandages from instep to knee.

Laboratory Work.—On May 18, 1947, the urine was negative except for a faint trace of acetone. The blood count on May 19, 1947, showed a hemoglobin of 11.6 grams (80%) with 4.2 million red cells. The white cell count was 22,500, with 92 segmented forms, 6 lymphocytes, 1 monocyte

and 1 basophile. On May 23, 1947, there was a reduction in the red cell count to 3.5 million and in the hemoglobin to 9.09 grams. The white blood cells remained about the same, both in number and differential count. By May 28, 1947, the hemoglobin had improved somewhat, having increased to 9.9 grams with no increase in the erythrocyte count. The leucocytes remained unchanged. The count on June 5, 1947, revealed a hemoglobin of 11.3 grams, with 3.2 million erythrocytes and 10,300 white blood cells, with 74 segmented forms, 25 lymphocytes, and 1 eosinophile. Tests for the Rh factor were positive, blood group 0, and the Wassermann reaction was negative. On June 6, 1947, heterophile antibody was found to be 1 plus in a 1:16 dilution. An x-ray film of the pelvis disclosed no abnormal findings in the bones or joints.

On discharge the patient had prominent abdominal collateral veins which were still present three months later. He developed dependent edema if legs were unsupported by his elastic stockings. Four weeks after discharge from the hospital the abdominal collateral veins were still prominent, especially on standing upright. There was slight edema on prolonged dependency when the elastic stockings were not worn. All the major peripheral pulses were palpable in both lower extremities. There was dependent cyanosis of the feet but no marked skin discoloration, perspiration, or other vasomotor phenomena seen in late stages of thrombophlebitis (Fig. 1).

The diagnosis was bilateral iliofemoral thrombophlebitis. The etiology was unknown but the onset may have been associated with the acute condition which has been described.

DISCUSSION

According to Ehrich and Krumbaar,[4] predisposition to iliofemoral thrombophlebitis is more likely based on a developmental rather than a congenital abnormality. Compression exerted upon the left common iliac vein by the right common iliac artery contributes to the production of developmental defects which predispose to deformity of the vein lumen. This probably accounts for the greater frequency of left- over right-sided iliofemoral thrombophlebitis. Extension of this process from the left into the right common iliac to produce the "horseshoe thrombophlebitis" is the usual course of events. Disappearance of the arterial pulsations in first the left and then the right lower extremity follows the spread of the thrombophlebitic process. It is interesting to note the absence of the distal pulses in the right lower extremity at the time when the process was confined to the left.

Therapy consisted of elevation of the foot of the bed on eight-inch blocks, warm fomentations, penicillin, 30,000 units every three hours, and paravertebral sympathetic nerve blocks. Bromsalizol was used in order to prolong the effect of the blocks and obviate the necessity for repeated blocking. The administration of a general anesthesia was necessary in order to carry out these blocks in a child.

The question of the use of anticoagulants was debated. Finally it was decided that this therapy should not be used for the following reasons: It would be extremely difficult to administer intravenous therapy in view of the scarcity of accessible veins. The daily prothrombin determinations required to adequately control Dicumarol in a child would be extremely difficult to obtain in view of the inaccessibility of venous blood. Such therapy, although well-standardized as to dosage in adults, has apparently not been very widely used in pediatric practice. If any anticoagulant had been selected, heparin rather than Dicumarol would have been the drug of choice. Possibly the new intramuscular preparation of heparin in Pitkin's menstruum, described by Loewe and Hirsch,[5] might have

offered a means of administering heparin in this case. The use of heparin in Pitkin's menstruum was considered but discarded because the arms were so small and thin that there was no place into which to inject the heparin. The lower extremities were involved in the thrombophlebitic process. Introduction of heparin into these members might aggravate the existing thrombophlebitis. The transfusions were administered as a means of supportive therapy and in order to overcome the thrombophilic tendency which exists in the presence of anemia.

This patient has had elastic stockings made to his measure and will continue to wear them until dependent edema no longer develops. He may subsequently develop superficial varicosities in his lower extremities which can be handled in the usual manner after the deep circulation has been re-established.

SUMMARY

A case of bilateral nontraumatic iliofemoral thrombophlebitis in a 6-year-old child is presented. The etiology, management, and prognosis of this case are discussed.

ADDENDUM

The following observations were made on a follow-up visit May 15, 1948. General health was very good. There were no complaints. The edema of the lower extemities had subsided completely. Supporting bandages were no longer required. The superficial veins of both lower extremities were normal. There were no obvious varicose veins. The abdominal collateral veins were still quite prominent.

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HEMIPLEGIA FOLLOWING CAROTID SINUS STIMULATION

A Case Report

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A CASE report of hemiplegia following trauma to the contralateral carotid sinus is brought to the attention of the reader, as there are only a few authentic cases of this nature.

CASE REPORT

A 60-year-old carpenter was on his knees boring a hole in a floor with a brace and bit when, as the bit suddenly went through the floor, he struck the right side of his neck against the end of an upright pipe. The site of injury was just beneath the angle of the right mandible. Approximately three minutes after this accident the left upper extremity exhibited clonic convulsive movements for a very short while. He did not lose consciousness and was able to continue work with his right hand. Approximately ten minutes after the accident, his wife found him in an adjacent room and observed that he was not able to use either the left upper or the left lower extremity. He was also somewhat confused. Further history obtained from his wife and brother revealed no evidence of pre-existing disease, hypertension, or declining health.

Physical examination revealed a man who was confused and kept his head turned to the right side. The muscles of the left side of the face were flaccid. The pupils and ocular fundi showed no abnormalities. The neck was not stiff and there was no swelling or discoloration at the site of injury. The blood pressure was 144/90. The heart rate was 48 per minute and the rhythm was regular. No heart murmur was heard. The radial pulses were equal and synchronous. The livei and spleen were not felt. On the left side the deep reflexes were absent and the muscles were flaccid. Urinalysis was normal, the red blood cell count and hemoglobin showed a slight degree of anemia, and the white blood cell count was slightly elevated with a normal differential. Spinal fluid pressure was not increased, the cell count was 5, protein was not increased, and the Kahn test was negative. A serologic test for syphilis (Kahn) was likewise negative. Electrocardiogram revealed no abnormalities.

The patient's temperature remained normal throughout his two weeks' stay in the hospital. He showed slight improvement in his ability to use the left lower extremity during the latter part of his stay in the hospital. When seen one year after the accident, his general state of nutrition was good. He recognized the author as the one who attended him while in the hospital although he was still not mentally alert after one year. The chief neurologic signs of significance at that time were confined to the left upper and left lower extremity. These consisted of spasticity of the muscles, hyperactive reflexes, grasp reflex, ankle clonus, and Babinski's sign.

DISCUSSION

Although aware of the numerous causes of hemiplegia in a 60-year-old man, one was immediately impressed by the sequence of events which followed injury

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in this case. The site of the impact was in the region of the right carotid sinus. Within three minutes following the blow, clonic convulsive movements developed in the contralateral upper extremity. Within ten minutes after injury, hemiplegia of the contralateral side was present.

The fact that the patient received a blow rather than manipulation of the carotid sinus should not distract from the assumption that carotid sinus stimulation was the cause of the subsequent events. It is postulated that the impact to the region of his right carotid sinus reflexly produced cerebral arterial constriction, manifested by the clonic convulsions of the left upper extremity. The arterial constriction was most likely followed by occlusion of a branch of the right anterior cerebral artery. Cerebral arteriosclerotic changes may well have contributed to this accident. The cases reported by Marmor and Sapirstein[1] showed peripheral and retinal arteriosclerosis as well as cerebral arteriosclerosis. Three of the cases reported by Askey[2] had arteriosclerosis. What role the hemodynamics, other than the local alterations caused by cerebral arterial constriction, contributed to the formation of a cerebral vascular thrombus is difficult to say. Although temporary asystole, bradycardia, or a decline in blood pressure may occur following carotid sinus stimulation, and thus may enhance the formation of a cerebral arterial thrombus, local cerebral phenomena may appear following carotid sinus stimulation without evidence of systemic circulatory changes.[2,3]

SUMMARY

1. A case report is given of a patient who developed hemiplegia shortly after receiving trauma to the contralateral carotid sinus.

2. It is postulated that his first symptoms resulted from cortical ischemia due to localized cerebral arterial constriction of reflex origin; furthermore, that thrombosis of the right anterior cerebral artery occurred and resulted in hemiplegia which was still present one year after the accident.

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Abstracts and Reviews

Selected Abstracts

Hand, A.: Cerebral Abscess; A Complication of Congenital Cardiac Disease (Fallot's Tetralogy). J. Pediat. 31:662 (Dec.), 1947.

A 4½-year-old cyanotic boy developed an upper respiratory infection, temperature, bradycardia, headache, vomiting, and convulsions. Brain abscess was suspected and trephination in the left temporal region permitted the evacuation of 42 c.c. of yellowish-green turbid fluid. The child died two days later.

Pulmonary stenosis, interventricular septal defect, and hypertrophy of both ventricles were found at necropsy. There was no mention of dextroposition of the aorta. Three separate brain abscesses were found: one in the left temporosphenoidal region, another in the left occipital lobe, and the third in the left parietal area. Attention is drawn to the frequency of brain abscess as a complication of congenital heart disease.

HAUB.

Shumacker H. B., Jr., Abramson, D. I., and Lampert, H. H.: The Use of Anticoagulants in the Surgery of Aneurysms and Arteriovenous Fistulas, With Particular Reference to Dicumarol. Surgery 22:910 (Dec.), 1947.

The authors presented their experiences with the use of anticoagulants in the prevention of thrombosis following various types of repair of peripheral arterial and arteriovenous fistulas. In a number of cases, dicumarol was given before operation, with the result that at the time of surgery an adequate reduction in prothrombin level had already been attained. Despite this, no particular difficulty with hemostasis was experienced in the operative field. As a safeguard, fibrin foam was often placed in the wound. In several cases, however, some later complications occurred, such as hematoma formation. Nevertheless, the authors expressed the opinion that reparative procedures upon peripheral arteries can safely be undertaken when a full anticoagulant effect has already been achieved with heparin, dicumarol, or both. Furthermore, they believed that they had obtained at least suggestive evidence for the view that such therapy renders less likely thrombosis of the repaired segment of artery.

ABRAMSON.

Watson, W. L.: Pulmonary Arteriovenous Aneurysm. A New Surgical Disease. Surgery 22:919 (Dec.), 1947.

The author described a rare condition, nontraumatic pulmonary arteriovenous aneurysm, consisting of a lobulated, thin-walled, branching, pulsating pulmonary sac of varying size, made up of both an arterial and a venous component. This structure produces a shunt in the lung whereby a considerable amount of blood passes from the arterial to the venous portions of the pulmonary circuit without passing through the alveolae of the lung to be oxygenated. This results in a low oxygen saturation of the arterial blood in the systemic circulation and the various changes consequent to such a condition.

On the basis of ten previous reports of such cases and two of his own, the author presented the pertinent points upon which a diagnosis of pulmonary arteriovenous aneurysm can be made.

All but two cases were men, most of the reported ages falling between 17 and 30 years. Persistent cyanosis of the face, hands, and feet, clubbing of the fingers and toes, and high red blood count and hemoglobin were common findings. Half of the patients complained of exertional dyspnea, but the heart, electrocardiogram, and blood pressure were not abnormal. X-ray films in each instance showed a branching, lobulated mass of uniform density in the lung field. Other diagnostic features were hemoptysis, epileptiform seizures, a normal spleen, and normal sternal puncture studies.

Polycythemia vera was ruled out by the age of the patient, the lack of splenomegaly, and a normal range of white blood cell and platelet counts. The absence of a history of exposure to high altitude or poisoning by heavy metals or aniline dyes eliminated the possibility of secondary polycythemia. Similarly, cardiac anomalies with a right to left shunt or chronic pulmonary disease preventing adequate oxygenation were ruled out by roentgenographic and electrocardiographic findings.

In the treatment of the condition, repeated venesections, phenylhydrazine, and surgical intervention have been employed. In the author's two cases, ligation of the artery feeding the aneurysm was carried out in one case, and in the other, the involved portion of the lung as well as the aneurysm were excised. The results in both cases were quite satisfactory; the high hematocrit, red blood cell volume, and the arterial oxygen saturation returned to normal.

ABRAMSON.

Blackford, L. M.: Calcification of the Myocardium. Ann. Int. Med. 27:1036 (Dec.), 1947.

Nine years before death, a 59-year-old white man had suffered an acute myocardial infarction due to thrombosis of the left anterior descending branch of the left coronary artery. He remained relatively asymptomatic following this episode. Death was due to the rapid development of left ventricular failure and a terminal thrombotic occlusion of the right coronary artery. At necropsy, the significant findings consisted of the following: The anterior surface of the left ventricle and the apex felt like bone. The pericardium was plastered against this part of the heart and there were also adhesions between the heart and the diaphragmatic surface of the pericardium. The anterior descending branch of the left coronary artery had been obliterated about 2 cm. below the bifurcation. Distal to this point, the heart was ballooned out to form a ventricular aneurysm and the myocardium was largely replaced by calcific bonelike material. The infarcted area was roughly circular, 8 cm. in diameter; its inner surface was rough.

WENDKOS.

Glaser, R. J., Dankner, A., Mathes, S. B., and Harford, C. G.: Effect of Penicillin on the Bacteremia Following Dental Extraction. Am. J. Med. 4:55 (Jan.), 1948.

Since the bacteremia which often follows dental extraction is believed to be of importance in the pathogenisis of subacute bacterial endocarditis, the authors have attempted to evaluate the efficiency of penicillin as a prophylactic agent in preventing such bacteremia. The results in a control series of forty patients are compared with those in a group of forty patients who received 600,000 units of penicillin in divided doses during the twenty-four hours preceding extraction. It is apparent from the results that penicillin, while effective in reducing the incidence of bacteremia after tooth extraction, did not prevent its occurrence in a large number of patients. It is suggested from the data that it may be desirable to extract teeth singly when penicillin prophylaxis is indicated.

WOODS.

Mufson, I., Quimby, E. H., and Smith, B. C.: Use of Radioactive Sodium as a Guide to the Efficiency of Drugs Used in Treatment of Diseases of the Peripheral Vascular System. Am. J. Med. 4:73 (Jan.), 1948.

Utilizing the radioactive isotopes of sodium according to the method of Smith and Quimby, the authors have studied the effects of drugs used in the treatment of peripheral vascular disease.

The radioactive material was introduced into the circulation by intravenous injection and its accumulation in the extravascular fluid in an extremity noted with a Geiger counter. This accumulation is dependent upon the patency of the minute vessels, the vascularity of the area, and the permeability of the capillary endothelium. An acceleration in rate should therefore be indicative of dilatation of the minute vessels and an increase in available semipermeable membrane.

Of the drugs tested, only histamine appeared able to produce an immediate increase in capillary diffusion rate as determined by a radiosodium curve taken following a single dose. Intra-arterial injection or iontophoresis are said to be the most efficient routes for the introduction of histamine in these tests. Neither papaverine nor 5 per cent sodium chloride given intravenously produced changes in the radioactive sodium curves.

WOODS.

Wagner, B. M.: Penicillin Therapy in Subacute Bacterial Endocarditis. Am. J. M. Sc. **215**:84 (Jan.), 1948.

This article contains an analysis of reports in the literature of the treatment of 521 cases of subacute bacterial endocarditis with penicillin. Clinical arrest was effected in 371 patients (71.3 per cent) who have continued to remain well. In an additional ninety-five patients (18.2 per cent), a "cure" was produced in the hospital, but the disease recurred and the patients died within three to four months. No autopsies were performed in this group. The remaining fifty-five cases (10.5 per cent) were complete clinical failures.

The following principles of treatment were considered to be amply justified by this composite experience: 1. The sensitivity of the infecting organism to penicillin should be determined in vitro within a range of 0.1 to 1 unit per cubic centimeter. 2. If the organism is sensitive, the dosage of penicillin should be 500,000 units daily by continuous intravenous drip. 3. All cases should be treated as early as possible. 4. Therapy should be continued for at least twenty-eight days. If the patient's condition does not improve, 1,000,000 units should be given daily for twenty-eight more days. 5. The plasma level of penicillin and the sensitivity of the organism to penicillin in vitro should be determined twice a week.

DURANT.

Plotz, M.: Progress of Medical Science: Non-Atheromatous Lesions of the Coronary Arteries. Am. J. M. Sc. **215**:91 (Jan.), 1948.

The most important disease of the coronary arteries is atheromatosis. Ninety to 95 per cent of all cases of myocardial infarction result from changes in and around an atheromatous plaque which result in reduction of the blood supply to the affected area. Other lesions of the coronary arteries are clinical curiosities and scant attention has been given to them. It is the purpose of this report to classify these changes and gather in one place the knowledge, especially in the way of recent advances, now scattered throughout the literature. Only the salient features are discussed, but most of the important late and key references are given for further study.

The following classification of non-atheromatous lesions is used as a basis for the review:

1. Congenital anomalies, including especially:
   - Single coronary artery
   - Origin from pulmonary artery (left coronary, right coronary, or both)
   - Origin of an accessory coronary artery from the pulmonary artery
   - Hypoplasia
2. Medial calcification with fibroblastic proliferation of the intima
3. Inflammatory lesions:
   - A. Specific infectious diseases
     - Syphilis
     - Tuberculosis
     - Other bacterial infections

B. Arteritis of unknown etiology
   Rheumatic fever
   Periarteritis nodosa
   Thromboangiitis obliterans

4. Aneurysms
5. Embolic and thrombotic disease
6. Neoplasm

DURANT.

Saphir, Otto, and Leroy, Elie P.: True Aneurisms of the Mitral Valve in Subacute Bacterial Endocarditis. Am. J. Path. 24:83 (Jan.), 1948.

In subacute bacterial endocarditis, mycotic aneurysms of the aortic and mitral valves are not rare. These are the result of erosion of a leaflet with cup-shaped deformity filled in with a layer of thrombotic material. A roughened necrotic valvular surface may eventually be covered with granular repair tissue, but in the course of this destructive and repair process, the valve may outpouch as a result of the force of blood current, and thus show a saccular deformity. Controversy exists as to the terms "false" versus "true" valvular aneurysm.

The writers noted twelve instances of valvular aneurysm in thirteen patients with subacute bacterial endocarditis. All were on the mitral valve. Five of these aneurysms were deemed to be "true" aneurysms, four of them on the anterior mitral leaflet and one on the posterior. They all were well circumscribed, with round, smooth outpouching of a part of the involved mitral leaflet. Gentle compression accentuated the aneurysmal outpouching, at the apex of which there was a small perforation in four instances. In one case, there were multiple small aneurysms. In all instances, the ventricular surface of the anterior (aortic) mitral leaflet was thickened and fibrotic. Small, round defects with thickened margins were the sites of the aneurysms, all of which bulged in the direction of the left atrium. These defects were really entrances, the aneurysm-depressions having a larger diameter. Thrombi and blood filled the depressions.

Microscopy revealed local thinning and loss of elastic lamellae of the zona ventricularis and reduction of the deeper zona fibrosa. Inflammatory cells infiltrated the area, and at the most involved point only the endothelial layer of the opposite side of the valve was intact.

The definition of a "true" aneurysm involves more than mere ulceration; granulation processes and scar formation with subsequent saclike outpouching constitute the lesion.

The writers point out an interesting clinical correlation. These patients with valvular aneurysm received large doses of penicillin, sometimes in association with sulfonamides. The clinical course was accordingly more protracted. In this connection a review of the clinical data of Libman and Friedberg is of interest. Working in the prepenicillin era, they described aneurysmal defects of the mitral valve in subacute bacterial endocarditis in the protracted bacteria-free stages of the disease. Some spontaneous tendency to healing of lesions is definitely implied in that observation.

The modern treatment that has shown such striking curative effects will in some instances be nullified by the accompanying developments of fibrotic valvulitis, aneursym, and valve rupture.

GOULEY.

Fawcett, R. M.: Myocardium After Sulfonamide Therapy. Arch. Path. 45:25 (Jan.), 1948.

This study was stimulated by recent reports in the literature indicating that sulfonamide therapy was the cause of interstitial myocarditis, which, at least from the standpoint of microscopy, was far more extensive than generally realized. Fawcett emphasizes that whereas sulfa drugs have been widely used, and sensitivity to such therapy has been definitely established in some patients, the clinical incidence of interstitial myocarditis is no greater than in the presulfonamide era.

Using as a criterion that type of cardiac involvement known in the literature as Fiedler's myocarditis or idiopathic myocarditis, the author points out that at the Mayo Clinic there has

been no increase in such myocardial involvements in comparing two five-year periods, one before and one after the common use of sulfonamides. Gross examination of hearts in the first period previous to 1935 and of hearts in the later period from patients who had received sulfonamide therapy, revealed no changes that might be attributed to therapy. Microscopic examination of hearts from the two periods showed no significant or constant differences between the control group and those patients who had received sulfonamide drugs in large amounts. Within each group there was a great variation of myocardial fiber damage and cellular infiltrations.

The author then examined 100 cases in which there had been sulfonamide therapy, including thirty subjected to massive dosage. There were in addition two patients who were found sensitive to the drug and who were known to have an interstitial myocarditis. This large group was matched with an equally large control group in which many patients died of infection but who had not been similarly treated. All cases with myocardial involvement due to rheumatic fever, diphtheria, syphilis, and myocardial infarction, and those with more than moderate coronary artery sclerosis were excluded. The numbers and types of the infiltrating cells in the heart sections were recorded in every case. Since the sections were of varying size, the quantitive estimate could not be accurate, but this handicap was common in both groups.

A comparative study of the sulfonamide-treated group and the control group showed no significant difference in the grading of cell types or of the increase of such cells infiltrating the myocardium. No significant difference could be found in the number of cells of any type, either in the auricular or the ventricular myocardium. This included eosinophilic infiltration, which has been stressed by previous writers.

In thirteen of twenty cases of the sulfonamide group in which the history suggested drug sensitivity, there was no increase in cellular infiltration; in only one of the twenty was there a plus 3 cellular infiltration.

All of the sulfa drugs currently used from 1935 to 1940, from sulfanilamide to sulfadiazine, were represented in this report which sharply negates clinical impressions and previous studies, dealing with "sulfonamide myocarditis."

GOULEY.

Maynard, R. M., and Thompson, C. W.: Congenital Aneurysm of an Aortic Sinus. Arch. Path. 45:65 (Jan.), 1948.

The writers report a case of congenital aneurysm of the sinuses of Valsalva occurring in a 23-year-old white man who suddenly developed substernal pain which radiated down both arms and was accompanied by a state of shock. On the day following this attack, there were moderate fever, reddish colored urine, and continuous substernal pain accompanied by soreness in the upper part of the abdomen. The slightest exertion brought on dyspnea.

The blood pressure was 156/20 in both arms; a Corrigan pulse and a pistol shot femoral sound were noted. There was a systolic thrill to the left of the sternum, and to-and-fro murmurs were heard over the precordium, loudest in the tricuspid area. The spleen was not palpable. At no time was there a positive blood culture. The past medical history was irrelevant.

In view of the fever and leucocytosis, penicillin therapy was instituted. One week after the onset of this attack, it was clear that the patient was suffering from congestive heart failure which was verified by marked prolongation of circulation time, by high venous pressure, and by x-ray study. The patient's condition gradually grew worse and death occurred eighteen days after the acute onset.

Necropsy revealed a right hydrothorax, but only a small amount of pulmonary edema. The heart was of slightly increased weight and showed a patency connecting a deficiency in the posterior sinus of Valsalva with a sacular outpouching into the right atrium. This sacculation was situated at the annulus fibrosus in the area of the medial leaflet of the tricuspid valve. The sac opened widely into the atrium. The other valves were normal. The foramen ovale was closed. The interventricular septum was intact. The pulmonary aorta was normal. The liver showed a nutmeg mottling throughout.

Microscopic examination revealed no inflammatory reaction in the wall of the aneurysm nor of the patency extending into the right auricle. The aortic wall showed nothing of note. The

lungs showed edematous interstitial tissue and in some areas large numbers of neutrophils. The spleen was normal.

It is believed that the severe chest pain and shock were caused by rupture of a congenital aneurysm. The electrocardiographic examination did not yield data of diagnostic importance.

GOULEY.

Larkin, M. A.: Abdominal Symptoms in Sudden Acute Heart Conditions. Am. J. Surg. 74:49 (July), 1947.

The author begins with a discussion of the visceral afferent innervation of the heart and the abdominal organs. The visceral afferent impulses course through the thoracolumbar sympathetic chain and, therefore, "it is evident that pain sensation from two unrelated systems, the heart and upper abdominal contents, can bombard the spinal cord in two complete and identical segments."

Larkin then discusses ninety-two cases with acute cardiac conditions, all but one being the result of coronary occlusions. The mortality for the entire group was 53.3 per cent. Twenty patients had abdominal symptoms which included pain, nausea, and vomiting. Seven of the twenty experienced abdominal pain only and six had only nausea and vomiting. Seven patients of the group suffered from abdominal pain and nausea and vomiting. Larkin cites a case history in which an exploratory laparotomy was performed for a suspected perforated ulcer in a 34-year-old white man. Death occurred on the second post-operative day and autopsy showed a rupture of the posterior wall of the left ventricle secondary to thrombosis of the right coronary artery and also a benign duodenal ulcer.

The author closes by discussing the differential diagnostic aids which may distinguish between an acute condition of the heart and one in the abdomen. These include the blood count, electrocardiogram, and the flat x-ray plate of the abdomen.

LORD.

Lindroth, L. V.: Sympathetic Nerve Block in Hypertension and Allied Cases. Am. J. Surg. 74:66 (July), 1947.

The author describes his technique of injecting absolute alcohol paravertebrally from the ninth through the twelfth thoracic sympathectic ganglia in two stages in the treatment of hypertension. General anesthesia is employed. Four cases are tabulated and the history of one patient is outlined. The advantages of the procedure over surgical thoracolumbar sympathectomy are the ease of performance, the slighter trauma to the patient, and the opportunity it affords to treat seriously ill patients who could not survive surgical intervention.

LORD.

Langley, G. J., and Platt, R.: Hypertension and Unilateral Kidney Disease. Quart. J. Med. 16:143 (July), 1947.

The purpose of this paper is to formulate the indications for nephrectomy in hypertension. The authors collected ninety-three cases from literature and added ten previously unpublished cases.

In forty-seven cases, the blood pressure was restored to normal and remained normal for the period in which the cases were followed, usually more than a year. In thirty-seven cases, no significant reduction of the blood pressure followed the operation; in some cases, it was higher after the operation. In six cases, there was a significant fall in pressure, though not to normal. In thirteen cases, the result was doubtful because of inadequate data or short follow-up period.

Age, of itself, did not contraindicate operation. Of sixteen patients over 45 years of age, eleven were cured and five were unimproved by nephrectomy. In forty-eight cases in which the retinal changes were studied, these changes appeared to have little prognostic significance. Of thirteen cases with a family history of hypertension, operation was successful in only one, whereas in thirteen cases in which the family history was stated to be negative, operation was successful in eight.

Of twenty-seven cases of pyelonephritis, seventeen had a successful result. Pyelonephritis was the lesion found in five cases with a positive family history of hypertension and in six with a negative family history. There were sixteen cases in which calculus was accompanied by pyelonephritis or hydronephrosis. Of these, operation was successful in only six. Of eighteen cases of hydronephrosis without stone, only four had a successful result.

In twenty-seven fully recorded cases in which the blood pressure failed to respond to nephrectomy, the operation was clearly indicated on surgical grounds in fifteen. Out of forty-six cases, there were obvious surgical indications for operation in seven. Thirty-three cases showed adequate evidence of unilateral disease, usually a functionless kidney. The main differences between the successes and the failures depended upon: (1) The possibility of reaching a sure diagnosis of unilateral disease; there was a higher incidence of certain diagnosis in the successful than in the unsuccessful cases. (2) A family history of hypertensive disease; such a history was more frequent in the unsuccessful cases. (3) The nature of the disease process; pyelonephritis and congenital abnormalities gave more favorable results than hydronephrosis or calculus.

BELLET.

Reid, G.: Observations on the Part Played by the Vasoconstrictor Substance of Blood Platelets in the Mechanism of Vascular Spasm. M. J. Australia 11:39 (Aug. 2), 1947.

This paper is concerned with determining whether vasuclar spasm may be produced by the vasoconstrictor substance of defibrinated blood or serum. Eight cats and four dogs were used. In no case did serum or defibrinated blood, when placed around the femoral or anterior tibial artery over lengths up to four centimeters, reduce the outflow from the hind limb. Likewise, no visible effect on the diameter of the vessel was observed. When serum in quantities of 0.5 to 2.0 ml. was injected intra-arterially into the cut stump of the lateral circumflex artery of nine cats and three dogs, including those which had shown no response to serum applied to the femoral artery, there resulted a sharp fall in the outflow from the hind limb, which, in the absence of a commensurable fall in systemic blood pressure or change in capacity, can be attributed only to vasoconstriction.

Ansethetic agent had no effect on the responses to serum. Again, it was thought that more marked effects might be produced if the circulation to the limb was occluded during and for some time after the intra-arterial injection. Occlusion of the common femoral or iliac artery by means of a clip for periods up to ten minutes after the injection of up to 5.0 ml. of serum had no effect in increasing or prolonging the vasoconstriction which was demonstrable after the circulation had been released, but usually the preliminary vasodilation did not occur. Occlusion of the main vessel did not affect the action of serum placed around the main vessel distal to the occlusion.

It was found that the placing of serum or defibrinated blood around the femoral artery produced no change in the diameter of the vessel whether the animal was given heparin or not. When an artery was divided in an animal which had received heparin, contraction of the vessel wall and hemostasis occurred, while the arterial blood pressure remained high. The results described so far lend no support to the view that the vasoconstrictor substance of serum is responsible for localized arterial spasm.

The main question for discussion is whether spasm, either locally or in the peripheral field of the damaged vessel, may be attributable to a humoral agent derived from blood platelets and present in shed blood. The author's experiments indicate that the humoral agent in shed blood is not responsible for localized arterial spasm. It may be a factor in maintaining constriction in the peripheral field of an artery, which has been damaged, thrombosed, or occluded by emboli, provided that the circulation is inadequate to remove it or that it continues to be liberated. A further possibility is that the effects of spasm in a damaged artery or simple mechanical obstruction of it may be aggravated by a peripheral constriction interfering with a collateral circulation.

The author concludes that vascular spasm may be attributable to either stimulation of nerve fibers in the wall of the vessel, resulting in constriction either directly or by reflex means, or to stimulation of smooth muscle by an adequate mechanical stimulus or by a humoral agent. The vascular constriction which results may be localized to a segment of artery or may involve its peripheral field or collaterals.

BELLET.

Nelson, W., Mayerson, H. S., Clark, J. H., and Lyons, C.: Studies of Blood Volume in Tetralogy of Fallot and in Other Types of Congenital Heart Disease. J. Clin. Investigation 26:800 (Sept.), 1947.

These authors determined the hematocrit, hemoglobin, total circulating hemoglobin, plasma protein, and total plasma protein, plasma volume, red cell volume, and bood volume in seven cases of the tetralogy of Fallot, in four cases of isolated interventricular septal defect, and in one case each of Eisenmenger complex, isolated pulmonic stenosis, coarctation of the aorta, congenital mitral stenosis, and patent ductus arteriosus.

It was found that the plasma volume in the tetralogy of Fallot, contrary to previous investigations, was not significantly nor consistently reduced but rather was normal or slightly increased; however, the red cell volume and total blood volume were markedly increased. The authors suggest that the factor in the tetralogy mainly responsible for this increased red cell volume is the pulmonary stenosis and not the septal defect, since patients with isolated septal defect and the Eisenmenger complex showed normal or slightly increased hemoglobin, red cell volume, and plasma volume whereas those whith isolated pulmonic stenosis had a high red cell volume and hemoglobin (not nearly as high as in the tetralogy) and slightly increased plasma volume. The pulmonic stenosis in the tetralogy forces about 75 per cent of the blood from the right ventricle into the systemic circulation instead of through the lungs. No explanation was found for the high red cell volume in isolated pulmonic stenosis since, in this anomaly, there is no oxygen unsaturation and, therefore, an absence of stimulus for the increased red cell production. Likewise, the reason for the high cell volume and plasma volume in patent ductus arteriosus and congenital mitral stenosis is not known, since the blood oxygen is not unsaturated in thses states.

The authors showed that the red cell volume and blood volume in tetralogy diminished with bed rest and after the Blalock operation. They believe the determinations made by them are useful in diagnosis of congenital heart disease; in deciding when to operate in tetralogy; and as a measure of the beneficial effects of the surgical procedure.

WAGNER.

Danowski, T. S., Winkler, A. W., and Elkinton, J. R.: Biochemical and Hemodynamic Changes Following the Subcutaneous Injection of Glucose Solution. J. Clin. Investigation 26:887 (Sept.), 1947.

The authors state, "it is well known that the loss of extracellular electrolyte such as occurs in Addison's disease, etc., may contribute to cardiovascular collapse." If this loss is acutely induced it results in a state of shock. It seemed probable that during absorption of glucose given by hypodermoclysis salt is removed from the circulation into this subcutaneous pool in a manner identical with that observed following the injection of fluid intraperitoneally.

This situation was studied experimentally in two dogs and in four patients. In dogs, it was possible to induce salt depletion and shocklike states, with a diminished plasma volume and extracellular fluid volume and increased hematocrit and plasma protein by giving nonelectrolyte glucose solutions subcutaneously. A similar finding was obtained in one patient. In the three other patients there were similar changes, but of a lesser magnitude so that shock was not observed. These changes were not observed when the nonelectrolyte glucose solution was given intravenously.

The authors believe that the salt depletion by subcutaneous administration of nonelectrolyte glucose solutions may precipitate shock if a large quantity is given over a short period of time and if the previous condition of the patient's hemodynamics is bordering on shock. They suggest treatment of the latter state with electrolytes and blood or blood substitutes before administering nonelectrolyte glucose solutions subcutaneously.

WAGNER.

Lenzi, S.: On the Wolff-Parkinson-White Syndrome. Cuore e circolaz. 31:141 (Sept. Oct.), 1947.

The author presents six cases of the Wolff-Parkinson-White syndrome and reviews all theories which have been advanced in order to explain this electrocardiographic picture. He attempts

to divide the cases into two groups. In the first group, the author places cases with organic lesions of the heart; in the second, those with a normal heart. While the syndrome in the latter group of patients could be explained by the theory of pre-excitation, the occurrence of the syndrome in the former group of patients might be explained in various ways, including myocardial lesions, myocardial edema, and altered excitability of the two branches of the bundle of His.

LUISADA.

Pincelli, C.: On the Behavior of Serum Cholinesterase in Cardiac Patients Treated With Digitalis. Cuore e circolaz. 31:155 (Sept.-Oct.), 1947.

This study was prompted by the theory of Danielopolu that digitalis acts only as a parasympathomimetic drug and that its action is based on inactivation of serum cholinesterase. The author determined the serum cholinesterase in twenty-five cardiac patients in congestive failure, before and after digitalis. These patients presented low values of the cholinesterase before treatment and a sharp rise of cholinesterase after digitalis, if the action of this drug was clinically apparent.

Two alternative explanations of this fact are advanced. None of them seems to confirm the parasympathomimetic theory of Danielopolu.

LUISADA.

Engel, G. L., and Romano, J.: Studies of Syncope: IV. Biologic Interpretation of Vasodepressor Syncope. Psychosom. Med. 9:288 (Sept.-Oct.), 1947.

The authors present the concept that vasodepressor syncope results when the primitive reflex preparation for flight or struggle is initiated but then, for some reason, appropriate action becomes impossible or must be inhibited. They describe the physiologic changes occurring during vasodepressor syncope as follows: decreased blood flow to the skin, initial accelerated pulse, increased respiration, sudden slowing of pulse rate, diminution of muscle tone, decrease of peripheral vascular resistance, and fall of blood pressure, which, when it reaches a critically low level, causes the patient to lose consciousness and fall. Vasodepressor syncope seems to occur in settings of real, threatened, or fancied danger when appropriate action is inhibited or impossible. The most common example is the faint following venipuncture. Pain and response to injury may also lead to vasodepressor syncope.

BELLET.

Wendholz, F., and Grayson, C.: Roentgen Demonstration of Calcifications in the Interventricular Septum in Cases of Heart Block. Am. J. Roentgenol. 58:411 (Oct.), 1947.

The mitral annulus fibrosus is not a complete ring. It encircles the mitral ostium on three sides, being absent at the root of the aorta, and ends on either side in a fibrous nodule, the trigona fibrosa. The ring is completed by a system of fibers from the trigonum fibrosum and is reinforced by bundles from the fila coronaria. This explains why, in a large majority of cases, calcarious deposits in the mitral annulus fibrosus are shaped like the letters *C*, *J*, or *U*. If a completely calcified ring is present, then not only the metral annulus but also the fibrous trigones and the space between them are involved.

Calcium deposits in the valves, annulus fibrosus, and adjacent fibrosus tissue occur in 7.5 to 8.7 per cent of all autopsies. The deposits are usually first seen in the posterior third of the mitral ring with extension toward the right trigonum and the septum. In the latter region there is a division, with one extension going into the trigonum and the other into the posterior or lower portion of the membranous septum. With heavier calcification, there may be a continuation across the space between the trigones into the opposing portions of the trigona and into the adjacent bundles of the aortic ring and fila coronaria. In these cases a complete or crescentic ring is formed around the mitral ostium.

Calcifications in the aortic area begin at the root of the valves. Caudad extensions from the right semilunar valve usually involve the membranaceous septum. Calcifications of the septum are first located in the region of the bifurcation of the conduction bundle and then in the region

of the crus commune. The bundle itself usually is displaced, then stretched, degenerated, and finally calcified.

By means of careful roentgenoscopic examination, the position for best visualization of the involved valves was determined and corresponding roentgenographic exposures were made. Three types of roentgen signs were recognized that were indicative of the presence of calcification in the membranaceous septum:

(1) Caudad extension of calcium shadows from calcified aortic valves or rings. The authors observed two cases which were associated with heart block. No case with such extension was observed in which heart block or prolonged conduction time was not recorded.

(2) Complete circular or crescentic calcification about the mitral ostium. Eight complete ring calcifications were observed in twelve cases of heart block and in two of twenty-one cases without heart block.

(3) Incomplete mitral ring calcifications with nodular thickening of calcareous deposits at the right end of the posterior branch of the calcified mitral ring. This type of calcification was found almost as frequently in those cases without as in those with heart block.

ZION.

Leigh, E., and Hazelton, A. R.: Six Cases of Cardiovascular Disorder With Peripheral Neuritis. Brit. M. J. 2:573 (Oct. 11), 1947.

Six cases were chosen from among many men suffering from a common group of symptoms in a prisoner-of-war camp in Siam. The typical symptoms were breathlessness on slight exertion, palpitation, and occasional precordial pain. On examination, tachycardia, abnormal increase of pulse rate on rising from recumbent to upright position, tumultuous heart action, some impurity of the first sound at the mitral area, a pistol shot sound over the femoral artery, and carotid sinus irritability were present. The clinical picture resembled that of the effort syndrome. No cardiac enlargement, edema, or anemia was detected. Reduced sensibility of peripheral distribution to pinprick and deep pressure, sluggish reflexes, and a slight Romberg sign constituted the common neurological findings. Following therapy, abnormalities in physical signs in the heart showed improvement in four out of the five cases in which such signs were present. Carotid sinus irritability disappeared in two out of three cases. The improvement in symptoms began after the third injection of thiamin chloride.

BELLET.

Doniach, I.: Uremic Edema of the Lungs. Am. J. Roentgenol. 58:620 (Nov.), 1947.

A proportion of uremic hypertensive patients with lift ventricular failure develop a subacute pulmonary edema which may be transitory. The roentgen findings consist of a fine or coarse mottling, spreading out from both hilar regions and leaving a clear zone at the apices, periphery, and bases. This distribution, rather than the nature of the mottling, appears to be typical of subacute pulmonary edema associated with uremia and hypertensive heart failure. This intensive roentgen change is usually out of proportion to the local clinical signs and symptoms, which may be minimal apart from the dyspnea. There is no obvious correlation of the onset of edema with any one of the uremic biochemical findings such as hypoproteinemia or acidosis.

In fatal cases, the most significant change seen in the lungs is a "solid edema" due to a fibrinous or an albuminous intra-alveolar exudate. This exudate is believed to result from a combination of a rise in pulmonary capillary pressure secondary to left ventricular failure and an alteration of capillary permeability resulting from uremia.

In nonfatal cases, the lung changes appear with the onset of failure and resolve with the relief of failure. The blood urea level remained constant in at least one of the cases cited by the author. In a series of fifty uremic patients selected at random and free from signs of heart failure, no roentgen signs of pulmonary edema were encountered.

The roentgen findings, though characteristic of uremic hypertensive heart failure, are not pathognomonic of this condition since these findings may be seen in other conditions of heart failure associated with capillary damage such as rheumatic fever or uncomplicated acute left ventricular failure.

ZION.

Maguire, C. H., and Griswold, R. A.: Further Observations on Penetrating Wounds of the Heart and Pericardium. Am. J. Surg. 74:721 (Nov.), 1947.

The authors report their experience with thirty-three cases of penetrating wounds of the heart and great vessels within the pericardium. Twenty-three of the patients lived long enough to reach the operating room. Two patients died postoperatively, one of cerebral embolism from mural thrombi on the third day and the other on the second postoperative day from secondary hemorrhage from the cardiac wounds. The cause of death was exsanguination in the ten patients who died on admission to the accident room or before exploration was possible.

Several points were stressed by the authors. A well-trained resident staff who are sufficiently familiar with wounds of the heart to make an accurate diagnosis and effect prompt operative treatment is essential. The operation should be carried out without delay, but careful preparation of the patient's skin and adequate scrubbing by the surgical team must not be neglected. Positive pressure oxygen with nitrous oxide is the anesthetic of choice. The most satisfactory incision is a transverse one near the site of the wound with resection of one costal cartilage and, if necessary for exposure, division of the adjacent costal cartilages. The wound in the heart or great vessel is sutured and if possible the sutures are not placed through to the endocardium. The pericardium is not closed but left open so fluid can flow into the left pleural space. No external drainage is employed. Postoperatively, one or two aspirations of the left pleural space are usually necessary.

Diagnostically, the triad described by Beck is helpful. A falling arterial blood pressure associated with a rising venous pressure in the presence of a quiet heart constitutes the triad. The authors point out that the general condition of these patients and the shock are out of proportion to the extent of the obvious wound. The wounds have usually been caused by three types of weapons: a knife, ice pick, or pistol.

LORD.

Stutzman, J. W., Murphy, Q., Allen, C. R., and Meek, W. J.: Further Studies on the Production of Cyclopropane-Epinephrine Tachycardia. Anesthesiology 8:579 (Nov.), 1947.

This study was undertaken to determine the site of action of cyclopropane in sensitizing the heart to injected epinephrine. The test dose of epinephrine which was injected intravenously varied from 0.005 to 0.01 mg. per kilogram but remained constant for any one experiment. In each case the dose was sufficient to produce ventricular tachycardia, lasting from fifteen to eighty-five seconds, in the intact anesthetized dog. First, preparations were made in which the body but not the brain was exposed to cyclopropane. Second, three crossed circulation experiments were carried out so that cyclopropane might be restricted either to the brain or to the remainder of the body.

In the first six animals both cyclopropane and epinephrine were restricted to the body circulation by clamping the cerebral blood supply. Each of these animals developed ventricular tachycardia and in three animals this immediately passed into ventricular fibrillation. Cyclopropane and epinephrine were likewise restricted to the body circulation of the recipient in crossed circulation experiments on two dogs. Again ventricular tachycardia was at once produced. Cyclopropane was allowed to reach the entire animal while epinephrine was restricted to the body circulation in three dogs. This also resulted in ventricular tachycardia.

In three of the animals which had previously had temporary occlusion of the cerebral circulation and in the three dogs in which crossed circulation experiments were performed, an anemic decerebration was induced by occluding the cerebral blood flow for thirty minutes. Cyclopropane and epinephrine were then restricted to the body circulation. In contrast to previous experiments, ventricular tachycardia was no longer produced. It was also found that there was no ventricular tachycardia with epinephrine injection when cyclopropane was allowed to circulate only in the cerebral circulation of the recipient.

From the results of these experiments it is evident that for the production of cyclopropane-epinephrine tachycardia cyclopropane and epinephrine do not have to reach the cerebral circulation, but certain brain centers must be intact and functioning. Furthermore, the addition of

cyclopropane to the cerebral circulation does not alter the duration of the cardiac irregularity. It appears, therefore, that the heart is reflexly sensitized by cyclopropane.

In an attempt to locate the afferent pathway of such a reflex the spinal cord was cut below the main cardiac sympathetic outflow. These experiments suggest that afferent impulses entering the cord below T 6 are involved in reflex sensitization of the heart. Bilateral supradiaphragmatic splanchnicotomy and sympathetic chain resection from T 9 to L 1 were done in fifteen dogs. This procedure afforded complete protection from ventricular tachycardia in thirteen of the animals. In the remaining two, a cord section of T 11 resulted in protection. It was found that bilateral adrenalectomy alone does not interfere with the production of ventricular tachycardia.

Additional experiments indicate that cyclopropane stimulated receptors located in the mesentery. A ventricular tachycardia could be prevented by removal of the mesentery to the ileum and jejunum.

The authors conclude that cyclopropane reflexly sensitizes the heart of the dog to injected epinephrine. The receptors are distributed for the most part throughout the peripheral 3 cm. of mesentery. Impulses travel by visceral afferent fibers through the celiac and superior mesenteric plexuses, splanchnics, and spinal cord to a brain center above the pons. Efferent impulses then pass to the heart by way of the cardiac sympathetics and increase the irritability of the heart.

BELLET.

Freeman, A. M.: Acute Postpartal Heart Failure, A Report of Four Cases With an Inquiry Into Pathogenesis. J. M. A. Alabama 17:163 (Nov.), 1947.

The author presents four cases of acute heart failure which appeared during the puerperium and which responded promptly and apparently completely to measures commonly employed in heart failure.

The heart failure occurred at term in two cases and three weeks and two months post partum, respectively, in two other cases. The precipitating factors were sudden increase in work after bed rest in two cases, and administration of intravenous fluids in the two other patients.

The author reviews the literature on this subject and emphasizes the increase in the work of the heart which occurs in pregnancy as an important factor in the precipitation of heart failure. Additional factors to this heart failure have been the occurrence of toxemia of pregnancy and the presence of hypertension and anemia.

BELLET.

Levy, T.: Case Report of Mechanical Right Heart Failure From Extension of an Undiagnosed Bronchiogenic Carcinoma. South. M. J. 40:892 (Nov.), 1947.

The patient, a 34-year-old man, had been short of breath for several months, especially on exertion. His acute illness began with a sore throat which lasted a week or ten days and was accompanied by an acute cold and cough. The cough continued and was accompanied by soreness in the left chest. Within the next few weeks a friction rub was heard in the right third intercostal space, anteriorly and laterally. The patient then developed a slight fever and was given 30,000 units of penicillin every three hours for ten days. Following this, he became afebrile. He developed rough systolic murmur which was loudest in the left interscapular region. The electrocardiogram revealed right axis deviation. He began to show signs of a severe grade of heart failure and reacted poorly to treatment. Death occurred about two months after the onset of acute symptoms.

The pertinent necropsy finding was the presence of a large oat-cell carcinoma, arising at the bifurcation of the trachea, extending through the pericardium, compressing the pulmonary artery, occluding the right branch by invasion, and resulting in right-sided heart failure.

BELLET.

Loewe, L., Hirsch, E., and Grayzel, D. M.: The Action of Heparin on Experimental Venous Thrombosis. Surgery 22:746 (Nov.), 1947.

The authors produced thrombosis in the jugular veins of rabbits. The veins were dissected free from the surrounding tissues and the proximal portion securely tied with a silk ligature. A

narrow ribbon retractor was placed under the vein distal to the ligature and the vein tapped briskly fifteen to thirty times with the handle of a scissors. Bleeding occurred from the veins but was controlled by gauze pressure. A clot which was visible and palpable usually formed. Heparin was instituted from one to fourteen days after trauma in an attempt to evaluate its effect on preformed thrombi. Heparinization was accomplished by administering heparin in Pitkin's menstruum. Heparin, 40 to 100 mg., was given every two to three days and no hemorrhages were observed in any of the animals. At regular intervals the jugular veins were exposed, removed, and examined microscopically in each group of animals.

Several facts were demonstrated: patency of a vein can be re-established, following clot formation, in a large number of experiments by means of adequate heparinization beginning as long as six days after the incident of trauma; the extent and speed of recanalization is enhanced by the use of heparin; in the presence of occluded veins the opening of adjacent collateral venous channels is extensive in the presence of heparin therapy.

Theoretical considerations are discussed in an attempt to explain the ways in which heparin is able to bring about the dissolution of relatively recent clots and to aid and abet recanalization and the formation of collateral circulation in older organized thrombi.

LORD.

Welch, K. J.: Failure of the Peritoneal-Button Operation for Ascites, Report of Two Cases. New England J. Med. 237:735 (Nov. 13), 1947.

The author reports his experience with two patients who were provided with peritoneal buttons and were ultimately subjected to post-mortem examination.

Case 1 is that of a 57-year-old man with a diagnosis of portal cirrhosis. The patient was admitted to the hospital for operation after a period of recurrent ascites lasting three and one-half months. Fifteen days after a glass peritoneal button had been inserted, he was discharged from the hospital with no evidence of reaccumulation of peritoneal fluid. However, less than one month after operation, fluid had reaccumulated so that he again required paracentesis. The patient died three months later after a massive gastrointestinal hemorrhage from the rupture of an esophageal varix. Post-mortem examination revealed a collapsed subcutaneous cystic space measuring 10 by 7 by 4 cm. which communicated with the peritoneal cavity.

Case 2 is that of a 46-year-old man, with a history of having consumed over a pint of whisky a day for many years. He was admitted to the hospital with a diagnosis of portal cirrhosis following four months of recurrent ascites that required frequent abdominal paracentesis. A peritoneal button was inserted, but in spite of this fluid continued to accumulate, and repeated paracenteses were again necessary. Five weeks later, at the time of death, a massive collection of ascitic fluid had again developed. Post-mortem examination revealed that the peritoneal layer blended evenly with the wall of the canal provided by the button and was continuous with the lining of the subcutaneous space.

In both cases, subcutaneous pockets, which had dense, hyalinized, connective tissue walls, communicated with the peritoneal cavity.

BELLET.

Duguet, J., Dumont, P., and Bailliart, J.: The Effects of Anoxia on Retinal Vessels and Retinal Arterial Pressure. J. Aviation Med. 18:516 (Dec.), 1947.

The purpose of this investigation was to study the effects of high altitude on the retinal vessels. The retinal circulation is relatively independent of the general circulation and has often been compared with the circulation of the brain. Changes in the retinal vessels were studied by photographing the retina, first, at ground level and then at various altitudes. The authors found that dilatation of the retinal vessels becomes noticeable and can be measured on photographs when an altitude of 4,000 meters is reached; dilatation increases with altitude and reaches its maximum at 6,000 meters, but does not increase after the subject has been at that level for fifteen minutes.

The authors also studied arterial pressure changes by Bailliart's ophthalmodynamometer. Their research was limited to ascertaining the changes of the retinal diastolic blood pressure in

anoxia, since its measurement is always more precise than measurement of the systolic pressure. Measurements were made on seven subjects, first, at sea level, then when conditions in the decompression chamber simulated an altitude of 6,000 meters, and, finally, after a period of at least fifteen minutes at this simulated level. Studies were repeated at the same simulated altitude while the subject breathed oxygen and again when he returned to the conditions at sea level. Ocular tension and systemic arterial pressure were also measured under similar conditions.

The findings show that, under the influence of altitude, variations of diastolic blood pressure in retinal arteries can be classified into two main types which are quite similar to the response of the systemic blood pressure to high altitude. In the first type the reaction to anoxia consists of a rise of retinal arterial pressure which is generally concomitant with a rise of systemic blood pressure and shows a tendency to return to normal values when the duration of the stay at this altitude is prolonged. In the second type of reaction, on the contrary, there is a fall of retinal arterial pressure which is accompanied by a fall of systemic pressure, systolic and diastolic, and which increases with the duration of the stay at this altitude. Patients who react in the latter way seem to have less resistance to anoxia than those who show the first type of reaction and may have a greater tendency to collapse. The authors are inclined to think that anoxic changes in retinal blood pressure are mainly the consequence of the manner in which the intracranial pressure reacts to the same abnormal conditions.

BELLET.

McMillan, R. L., and Welfare, C. R.: Chronic Auricular Fibrillation. J. A. M. A. 135:1132 (Dec. 27), 1947.

The authors studied fifty unselected cases of auricular fibrillation. Of the fifty patients, in forty-four (88 per cent) normal rhythm was restored and persisted from one month to two years in twenty-five (50 per cent). Forty-six per cent of the patients had rheumatic heart disease; 32 per cent had arteriosclerotic heart disease, and the remaining 22 per cent had thyrotoxic heart disease, hypertensive cardiovascular disease, or combinations of these conditions.

All patients were admitted to the hospital and observed for several days before quinidine treatment was begun. Repeated electrocardiograms were made before, during, and after quinidine therapy. Complete digitalization was effected in each case before quinidine therapy was instituted. An attempt was made to observe changes in cardiac efficiency, before and after reversion to normal rhythm, by daily measurements of vital capacity and by determinations of the venous pressure and circulation time. Roentgen studies before and after the restoration of normal rhythm failed to show consistent changes in the size of the auricles. In eighteen patients of the series, determinations of the vital capacity revealed an average increase of 270 c.c. with return to normal rhythm. In thirteen patients whose venous pressure was estimated, an average decrease of 20 mm. of saline solution was found after the return to normal rhythm. In fourteen patients, the circulation time decreased an average of 6.7 seconds.

In this series, failure to revert to normal rhythm bore little relationship to the degree of failure present, the age of the patient, or the duration of the fibrillation. In every case of thyrotoxic heart disease, treatment of the auricular fibrillation was unsuccessful until the underlying hyperthyroidism had been corrected. Five patients (10 per cent) of this series had thyrotoxicosis, either alone or in combination with advanced rheumatic heart disease. Two failures occurred (40 per cent). Three failures occurred in sixteen patients with arteriosclerotic heart disease (failure rate of 18.7 per cent); whereas in twenty-three patients with rheumatic heart disease, treatment was unsuccessful in only one case, a failure rate of 4.3 per cent. Fourteen patients with rheumatic heart disease have maintained a normal sinus rhythm for periods varying from four months to two years. Only 50 per cent of these patients are on maintenance doses of quinidine.

The patients in the 40- to 49-year age group stand out as having the most favorable course; 50 per cent of the twenty patients in this group have had regular rhythm for four months or more. Patients whose auricular fibrillation was abolished on doses of only 0.2 to 0.3 Gm. of quinidine sulfate every four hours are most likely to maintain normal rhythm. However, the necessity for huge doses does not preclude a favorable course. The etiology of the heart disease seems to be

the dominant factor in the success of treatment. Seventy-one and four-tenths per cent of the patients who still maintain a regular rhythm after four or more months had rheumatic heart disease. Eleven of the fifty patients studied have died. Four of these patients had had no quinidine for more than four days at the time of their death.

These authors feel that although the use of quinidine is attended by certain dangers, the incidence of serious cardiovascular accidents in patients treated with quinidine judiciously is little, if any, greater than in similar patients treated without quinidine.

BELLET.

Wilens, S. L.: The Relationship of Chronic Alcoholism to Atherosclerosis. J. A. M. A. 135:1136 (Dec. 27), 1947.

The purpose of this paper is to report the incidence of atherosclerosis in 519 persons 35 years of age or older, who were chronic alcoholics and who have been studied at necropsy. The findings in this group were compared with those in a control group of 600 consecutive necropsies on subjects 35 years of age or older at death, who were total abstainers or moderate consumers of alcohol.

In approximately one-half of the 519 alcoholics, the daily consumption of alcohol was known to have exceeded one pint of whisky, or its equivalent in other forms of alcoholic beverage, for many years. In the alcoholic group as a whole, atherosclerosis was considerably less common and less severe than in the control group of persons who consumed no alcohol or moderate amounts. Lesions that may be attributed to atherosclerosis of the coronary and cerebral arteries were only one-half to one-third as common in the alcoholic addicts as in the control series. However, in excessive alcoholics both severe and moderate degrees of atherosclerosis may develop with some frequency. Three-fourths of both men and women of the control series were 55 years of age or older at death. Only one-half of the alcoholic men and one-fourth of the alcoholic women survived beyond the age of 55 years.

The relatively low incidence of terminal hypertension or lack of evidence of antecedent hypertension as suggested by the low incidence of cardiac hypertrophy in the alcoholic group may have been an important factor. Diabetes was rare in the chronic alcoholics of this series. There were no striking differences in body weight in the two groups, but obese and underweight persons were more numerous in the nonalcoholic series. The 27.9 per cent incidence of cirrhosis in this alcoholic group was considerably higher than has been reported. The incidence of severe, moderate, and mild generalized atherosclerosis was 8.3, 33.1, and 58.8 per cent, respectively, in the alcoholic addicts with cirrhosis, and 14.4, 31.6, and 54.6 per cent, respectively, in the alcoholic addicts without cirrhosis.

Comparison of alcoholic men with hypertension with nonalcoholic men with hypertension revealed a higher incidence of severe atherosclerosis in the nonalcoholic group. Of the nonalchoholic hypertensive men, 24.6 per cent were obese; of the alcoholic hypertensive men, only 19.8 per cent were over weight. In the nonhypertensive groups, 73.5 per cent of the nonalcoholic but only 44.8 per cent of the alcoholic men were underweight.

Differences in incidence of atherosclerosis observed in alcoholic and nonalcoholic groups at necropsy were not considered to be the result of alcoholism, per se, but were considered to be attributable to associated differences in age, blood pressure, and nutrition. The low incidence of myocardial and cerebral lesions resulting from atherosclerosis in persons who were chronic alcoholics was considered to be attributable, to some extent, to factors of age and blood pressure. In the hypertensive group, however, both cerebral and cardiac lesions were somewhat more common in nonalcoholic persons than in persons who were chronic alcoholics.

The author concludes that the substitution of alcohol for a large portion of ordinary foods in the diet does not have an appreciable effect on the development of atherosclerotic lesions. The apparent low incidence of atherosclerosis observed in chronic alcoholism is explained by the relatively young age at death, the low incidence of hypertension, and a lesser tendency for lesions in the heart and brain to develop, particularly in the presence of hypertension. The impli-

cation of this finding is that the materials deposited in atheromatous lesions are not necessarily derived as such from ingested food but that they may be elaborated within the body from other substances.

BELLET.

Gubergrits, A. Y.: Occult Injuries to the Heart. Am. Rev. Soviet Med. 61 (Dec.-Jan.), 1947-1948.

This communication deals with twenty-six patients who managed to survive the lodgment of foreign bodies in the heart. This in the experience of the author is not rare and was observed in 0.5 per cent of all patients with penetrating thoracic wounds who were encountered in the rear evacuation hospitals. It was found that survival after heart injuries was more frequent when the lesion was caused by a splinter from aviation bombs and land mines. Splinters were localized in the large vessels in two cases and in the cardiac musculature in twenty-four cases. The muscle of the left ventricle was involved fifteen times, the wall of the right ventricle seven times, the wall of the right atrium once, and that of the left atrium once. In no case was the foreign body found within the cavities of the heart. In most cases the diagnosis of foreign body in the heart was missed at the medical aid posts. The correct diagnosis was made in evacuation hospitals in twenty of twenty-six cases.

The reason for overlooking foreign bodies in the heart lies in the emphasis on lung rather than on heart injuries. Too little attention, therefore, is paid to changes in density of the heart shadow which are particularly important for the detection of small metal splinters. Among the complaints of the patients, precordial pain ranked first. The pain was stinging, and occasionally oppressive and intermittent, but unlike anginal pain, did not radiate to the periphery. Palpitation was a common complaint and was present in all but five patients.

The diagnostic method of choice for the location of a foreign body in the heart is the x-ray examination. It is essential to ascertain by this method whether the foreign body is situated within the cavity, in the wall of the heart, or whether it lies near the cardiac shadow. Fluoroscopy is the most valuable method in the diagnosis of foreign body injuries of the heart.

The working capacities of these patients may be reduced but little by such an injury; in many instances no symptoms were initially present. In most instances, however, cardiac weakness became evident later.

BELLET.

Adelman, M. H.: Anesthesia in Surgery of the Patent Ductus Arteriosus. Anesthesiology 9:42 (Jan.), 1948.

The purpose of this paper is to report the author's experiences with the anesthetic problems incident to the surgical ligation of a patent ductus arteriosus in thirty patients. Ten patients had subacute bacterial endarteritis of the ductus. Twenty-nine patients had good cardiac reserve with no evidence of failure. One patient had heart failure with dyspnea and orthopnea of three months' duration. In the majority of cases the lung parenchyma was normal. There was no surgical manipulation or traction of pulmonary structures. The operation concerned itself only with the patent ductus and its associated great vessels. The operative procedure, per se, produced no cardiac disturbances or arrhythmias.

In one case Avertin-cyclopropane was used, in nineteen cases cyclopropane was the sole anesthetic agent, and in the ramaining ten cases, cyclopropane-ether mixtures were used, cyclopropane being the primary anesthetic agent. Cyclopropane offers the advantages of rapid induction and quiet, unstimulated respirations. The author has been adding small amounts of ether (15 to 25 c.c.) to cyclopropane; this has served to combat the tendency toward laryngospasm and cardiac arrhythmias which tend to result from cyclopropane alone. No cases of "cyclopropane shock" were observed. As for the depth of anesthesia, middle second plane was adequate.

The primary anesthetic problem is one common to all chest surgery when an open pneumothorax is produced. This consists in the prevention of "pulmonary decompensation" with excessively active movement of the diaphragm and thoracic cage, shifting of the mediastinum with

each phase of respiration, "pendelluft," hypoxia, and hypercapnia. The surgeon's prime request is for a "quiet chest," an open chest whose movements do not interfere with the surgical procedure. In the majority of cases a quiet chest has been attained by the use of cyclo-ether and irregularly intermittent positive pressure (approximate rate, 8 to 10 per minute) with full insufflation of the lungs about every five or six minutes. Other than cyclopropane arrhythmias and laryngospasm, which necessitated intubation in two cases, there were no anesthetic complications.

BELLET.

Wartman, W. B., and Hellerstein, H. K.: The Incidence of Heart Disease in 2,000 Consecutive Autopsies. Ann. Int. Med. 28:41 (Jan.), 1948.

This report is a statistical study of the incidence of heart disease in 2,000 consecutive autopsies performed over a five-year period. Sixteen per cent of the 2,000 subjects were under 5 years of age. Nine hundred eighty-four of the patients had a cardiac lesion, although not all of the lesions were sufficiently important to have contributed to death. One hundred forty subjects had rheumatic heart disease of which cases sixteen were complicated by subacute bacterial endocarditis. Two hundred seventy-one persons had hypertensive heart disease of which number the majority also had coronary artery disease. There were 272 cases of coronary artery disease without hypertension. Only seventy-seven patients with hypertension had simple uncomplicated enlargement of the heart.

Forty-nine persons with rheumatic carditis lived to be 45 years old or more. Thirty-four had an active process, of which nine were primary without evidence of previous rheumatic carditis. Twenty-five had acute verrucous endocarditis superimposed on a chronic process. The mitral valve was involved in every instance except in two cases where there was an isolated aortic valvular lesion.

Five-hundred two (51 per cent) of the total of 984 persons with heart disease had coronary artery disease. Of those with coronary artery disease, 160 persons had myocardial infarcts of which 111 were of relatively recent origin. A statistical breakdown of these 160 cases of myocardial infarction revealed the following: The infarcts were single in ninety-four instances and multiple in sixty-six. Regarding localization of the infarcts, the lesion was limited to the left ventricle in 134 cases, to both left and right ventricle in eighteen cases, to the right atrium alone in four cases, and to the right ventricle alone in four cases. In five cases, isolated infarction of the interventricular septum was present. The infarct involved the anterior and posterior portion of the left ventricle in 72 per cent and 28 per cent, respectively. Of the total number with anterior wall infarction, in 54 per cent of the lesion extended to involve the anterior half of the interventricular septum. Of the total number with posterior wall infarction, the lesion extended into the posterior half of the interventricular septum in 25 per cent. Lateral wall infarction, whether alone or in combination with infarcts in other locations, was relatively infrequent. Infarction of the myocardium was associated with actual occlusion of the nutrient coronary artery in 82.5 per cent. In 13.7 per cent there was disease of the coronary artery without occlusion. In 3.8 per cent myocardial infarction occurred without coronary artery obstruction or disease. In 16 per cent a coronary artery was found to be occluded without any infarction occurring distal to the point of obstruction. Most of the persons in this group had died within three hours of the earliest onset of clinical symptoms. Of the 160 persons with myocardial infarcts, 40 per cent had mural thrombi in direct contact with the infarcted area. Of the 111 with recent myocardial infarcts, acute fibronous pericarditis overlying the myocardial lesion was found in 28 per cent. Fifty-five per cent of the persons with intracardiac thrombi had occlusion of peripheral vessels from either thrombi or emboli. Ventricular aneurysm, as a complication of myocardial infarction, occurred in 22 per cent (thirty-five cases). Mural thrombi commonly occurred within the ventricular aneurysm. Of the thirty-five cases of ventricular aneurysm, twenty-five occurred in the anterior apical portion of the left ventricle, three in the posterolateral, and seven in the posterobasal portion of the left ventricle. Rupture of the ventricular aneurysm occurred in five of the thirty-five cases. There was also rupture of those infarcts unassociated with aneurysm in two instances. In the majority, the rupture occurred between two to seven days after the onset of clinical symptoms indicative of acute coronary artery obstruction.

WENDKOS.

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The Michael Reese Hospital Postgraduate School in Chicago announces that its Intensive Postgraduate Course for Graduate Physicians in Electrocardiography will be held August 16 through August 28. Presented by Dr. Louis N. Katz, the course will be open to beginning and advanced students and will include group and individual instruction. The tuition fee is $150 and the size of the class is limited. Interested physicians should address Dr. Samuel Soskin, Dean, Michael Reese Hospital Postgraduate School, 29th St. and Ellis Avenue, Chicago 16, Ill.

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Original Communications

ANALYSIS OF MALFORMATIONS OF THE HEART AMENABLE TO A BLALOCK-TAUSSIG OPERATION

Helen B. Taussig, M.D.
Baltimore, Md.

THE operation developed by Dr. Alfred Blalock for the treatment of pulmonary stenosis and atresia is designed to increase the circulation to the lungs. Therefore, it should be of benefit to any person whose primary difficulty is lack of adequate pulmonary blood flow, provided the structure of the heart is such that it can adjust to the altered circulation.

Experience has shown that a patient with a tetralogy of Fallot can adjust to these changes in the circulation.

The main purpose of this paper is to analyze the findings of diagnostic significance in patients with other malformations which have proven amenable to this operation, and to give a brief summary of the long-time results following this operation.

Between July, 1945, and July, 1947, in addition to individuals with the tetralogy of Fallot, forty-seven patients have been operated on for the alleviation of pulmonary stenosis or atresia. This group was composed of patients whose cardiac contours were similar to those of a tetralogy of Fallot but with electrocardiographic evidence of a left axis deviation, patients with dextrocardia with or without situs inversus, patients with partial rotation of the heart upon its axis, patients whose clinical diagnosis was "pure" pulmonary stenosis with an auricular septal defect, and patients with unusual arrhythmias. The number of persons and the mortality rates in the respective groups are shown in Table I.

The George Brown Memorial Lecture delivered at the 20th Annual Scientific Meeting of the American Heart Association, Atlantic City, N. J., June 7, 1947.

From the Department of Pediatrics of the Johns Hopkins University and the Cardiac Clinic of the Harriet Lane Home of the Johns Hopkins Hospital.

The overall mortality rate for the first 350 operations* on all patients of all ages with all types of malformations in which the clinical diagnosis was lack of adequate pulmonary blood flow was 19 per cent. Furthermore, in this series, among the children between 2 and 12 years of age with a tetralogy of Fallot on whom it was possible to use the subclavian artery, the operative mortality rate was less than 7 per cent. Table I shows that the operative risk is considerably greater in persons with the atypical malformations with pulmonary stenosis or atresia than in those with the tetralogy of Fallot.

Accurate diagnosis of these atypical malformations is extremely difficult. A person with a left axis deviation, with a dextrocardia with or without situs inversus, with an incomplete rotation of the heart on its axis, or with unusual arrhythmias presents an abnormality which is a definite specific entity. The only group in which the diagnosis is open to question is the group with "pure" pulmonary stenosis.

TABLE I. ATYPICAL MALFORMATIONS OF THE HEART WITH PULMONARY STENOSIS AND ATRESIA SUBMITTED TO A BLALOCK-TAUSSIG OPERATION

	NO.	DEATHS	MORTALITY
Malformation			
Left axis deviation	19	3	15%
Dextrocardia	12	4	33%
Slight rotation of heart	3	2	66%
"Pure" pulmonary stenosis	4	2	50%
Situs inversus with levocardia	3	1	33%
Abnormal rhythms			
Nodal rhythm	4	3	75%
Wolff-Parkinson-White syndrome	1	1	100%
Complete dissociation	1	0	0

The majority of patients whose cardiac contour is similar to that of a tetralogy of Fallot, but who present electrocardiographic evidence of a left axis deviation and left ventricular hypertrophy, suffer from defective development of the right ventricle combined with tricuspid atresia and pulmonary atresia. Those with a dextrocardia, with or without a situs inversus, and those with partial rotation of the heart comprise a variety of malformations, but of the abnormal location of the apex beat or of the abdominal organs there is no question.

The separation of malformations on the basis of arrhythmias may seem arbitrary. This is done because, in our experience, persons with a tetralogy of Fallot have a normal sinus mechanism and the occurrence of a nodal rhythm or of a Wolff-Parkinson-White syndrome is reason to doubt the diagnosis of a tetralogy of Fallot. Indeed, not one of the patients with an abnormal rhythm who died had a tetralogy of Fallot. Of the two who were improved by operation, the exact anatomic structure of the heart could not be established.

*In the subsequent 250 operations the mortality rate was less than 10 per cent.

The diagnosis of "pure" pulmonary stenosis, that is, a pulmonary stenosis without a ventricular septal defect, was based on the contour of the heart, the circulation time, physiologic studies, and cardiac catheterization. All four patients were severely incapacitated. It was hoped that the auricular septal defect would serve to direct venous blood from the right auricle to the left and thereby compensate for the lack of an over-riding aorta.*

Two of the patients in whom the diagnosis of "pure" pulmonary stenosis was made were improved by operation; the other two died. In one the diagnosis was confirmed at autopsy; in the other, the diagnosis was wrong. In the latter case autopsy revealed a tetralogy of Fallot with an aorta which over-rode the ventricular septum to such an extent that after operation there was difficulty in the expulsion of blood from the left ventricle; moreover, there was no auricular septal defect.

In order to determine the advisability of operation on a patient with any unusual malformation, attention is directed primarily to the criteria which have proved essential for the successful completion of the operation. There are six such criteria which must be met. (1) The primary difficulty must be lack of adequate pulmonary blood flow. (2) There must be a pulmonary artery to which the systemic artery can be anastomosed. (3) A systemic artery must be available to use for the anastomosis. (4) The difference in pressure between the systemic and the pulmonic circulations must be such that blood will flow from the aorta to the pulmonary artery. (5) The structure of the lungs must be such that the patient can survive the collapse of one lung and the occlusion of one pulmonary artery. (6) The structure of the heart must be such that it can adjust to the altered circulation.

The first two and the last two of these considerations are the primary concern of the cardiologist, as there is always a systemic artery and, provided the diagnosis is correct, the pulmonary pressure will be low. Errors in diagnosis have been made and high pulmonary pressure has been encountered. Consequently, this problem will be considered in detail in the differential diagnosis of lack of adequate pulmonary blood flow.

Lack of adequate pulmonary blood flow is indicated by various findings. The history may be of aid in that most of these children squat when tired. Clinical examination offers several clues. The purity of the second sound at the base is often significant. Reduplication of the second sound is in all probability caused by the asynchronous closure of the aortic and pulmonic valves and is, therefore, good evidence that both great vessels are of functional importance. Conversely, a pure second sound suggests that functionally there is but one great vessel. In the presence of pulmonary stenosis or atresia, so little blood reaches the lungs that, even with cardiac failure, pulmonary congestion rarely occurs. Indeed, pulmonary congestion is strong presumptive evidence of adequate pulmonary blood flow. For the same reason, the history of hemoptysis is always suggestive of excessive pulmonary blood flow. However, hemoptysis must be

*Recent experience has shown that a patient with "pure" pulmonary stenosis and an auricular septal defect may not be able to maintain compensation after operation.

differentiated from the bleeding caused by the rupture of dilated esophageal varices due to collateral circulation.

The existence of a pulmonary artery to which to anastomose the systemic artery is essential for the completion of the operation. This, however, may be impossible to determine with certainty prior to the thoracotomy. Various clues as to the existence of a pulmonary artery may be present. The persistent patency of the ductus arteriosus is clear evidence of the presence of a pulmonary artery. When a patent ductus arteriosus occurs in combination with pulmonary stenosis or pulmonary atresia, the continuous murmur of a patent ductus arteriosus is widely transmitted throughout both lungs and is well heard posteriorly both to the right and to the left. Such a murmur must, however, be differentiated from the continuous murmur which may result from collateral circulation. Usually the murmur of a patent ductus arteriosus is louder than that which results from collateral circulation and, in addition, there is a palpable thrill over the base of the heart. If the murmur is limited to one side of the chest, it is clear evidence that blood is directed only to one lung; hence, in all probability the circulation is not by way of the ductus arteriosus but is through a large vessel of the collateral circulation. Similarly, if the continuous murmur is audible only in a certain part of the chest, it is presumptive evidence that the murmur is due to collateral circulation. The continuous murmur indicates the continuous flow of blood to that lung; therefore, it is the opposite lung which is in greater need of increased circulation. Moreover, when the main pulmonary artery is absent, the entire circulation is necessarily through the pathways of collateral circulation. Such a patient may not be able to survive the collapse of the lung which has the better circulation. Consequently, if operation is to be attempted, it should be performed upon the side opposite to that over which the continuous murmur is audible.

Although Dr. Blalock has operated successfully on some patients believed to have a patent ductus arteriosus who also had reduced pulmonary blood flow, the accuracy of the diagnosis of a patent ductus arteriosus could not be verified because the operation was performed on the side opposite to that of the supposed ductus arteriosus. The other condition, namely, a continuous murmur originating from large vessels of collateral circulation in the absence of a pulmonary artery, has been verified at autopsy.

The density of the hilar shadows is of great importance. In infants with inadequate pulmonary blood flow, the lungs are exceptionally clear. In older children, if the collateral circulation develops by way of the posterior mediastinal vessels, the hilar shadows become exaggerated. Such shadows must be differentiated from those caused by large pulmonary vessels. A large pulmonary artery usually causes large blotchy shadows. Those caused by the minute vessels of collateral circulation are the result of an aggregation of innumerable small discrete shadows. Such shadows never show expansile pulsations. This single finding differentiates these shadows from those due to a large pulmonary artery in which there is high pulmonary pressure. The hilar shadows should also be evaluated in relation to the extent of the collateral circulation; the latter is

usually proportional to the polycythemia. Persons with a left axis deviation, however, frequently show denser hilar shadows than are seen with a tetralogy of Fallot and a corresponding degree of polycythemia. This is probably due to the fact that a left axis deviation is commonly associated with defective development of the right ventricle, tricuspid atresia, and pulmonary atresia; consequently, the development of collateral circulation is essential in order for the patient to survive the closure of the ductus arteriosus. The vast majority of children with a tetralogy of Fallot have pulmonary stenosis. It is only rarely that a patient with a tetralogy of Fallot and pulmonary atresia survives the closure of the ductus arteriosus. Consequently, the collateral circulation develops at a somewhat later age in a child with a tetralogy of Fallot and pulmonary stenosis than in a child with pulmonary atresia, and is correspondingly less extensive.

Special laboratory tests are of aid in doubtful cases. The most useful and and also the simplest of these is the exercise test developed by Dr. Richard Bing. Bing* has demonstrated that upon exercise patients with pulmonary stenosis or atresia show a fall in the oxygen consumption per liter of ventilation, whereas normal persons and most patients with a normally placed pulmonary artery (as, for example, an Eisenmenger complex) upon exercise show an increase in oxygen consumption per liter of ventilation. This simple test has proved of great help in the determination of reduction of pulmonary blood flow and in the differentiation of a tetralogy of Fallot from an Eisenmenger complex. The test does not, however, differentiate a tetralogy of Fallot from a complete transposition of the great vessels and should not have precedence over indubitable fluoroscopic evidence of increased pulmonary blood flow.

Angiocardiography may be of help in the visualization of the pulmonary artery. Failure to visualize the pulmonary artery does not, however, mean that the pulmonary artery is absent. In our experience in cases of extreme pulmonary stenosis, not infrequently too little radiopaque substance passes into the pulmonary artery to visualize it. Obviously, if there is atresia of the pulmonary orifice, no dye will pass into the pulmonary artery; nevertheless, in the majority of cases the pulmonary artery beyond the point of atresia, although small, is normally formed and can be used to direct blood to the lungs. In general the larger the aorta, the smaller is the pulmonary artery. Nevertheless, even in some instances of a truncus arteriosus in which the circulation to the lungs is by way of the bronchial arteries, there is a vestigial pulmonary artery which ends blindly but is of sufficient caliber to permit the anastomosis of a systemic artery to it. Therefore, in the last analysis it may not be possible to determine the existence and the size of the pulmonary artery without thoracotomy.

Catheterization of the heart is of great help in the determination of pulmonary stenosis when it is possible to catheterize the pulmonary artery and

*Bing, R. J., Vandam, L. D., and Gray, F. D., Jr.: Physiological Studies in Congenital Heart Disease. I. Procedures. II. Results of Preoperative Studies in Patient With Tetralogy of Fallot. Bull. Johns Hopkins Hosp. 80:107, 121, 1947. III. Results Obtained in Five Cases of Eisenmenger's Complex. Bull. Johns Hopkins Hosp. 80:323, 1947.

measure the pulmonary pressure. However, in the presence of pulmonary atresia this is manifestly impossible.

Nevertheless, if there is clear evidence that the primary difficulty is reduction in the pulmonary blood flow, exploratory operation is indicated, provided the evidence at hand indicates that the size and structure of the heart are such that it can adjust to the altered circulation.

There are four primary considerations in regard to the structure of the heart. First, venous blood must be directed to the systemic circulation; second, oxygenated blood must be able to reach the aorta; third, the structure must be such as to permit the continuous circulation of blood at an accelerated rate; and fourth, the cardiac reserve must be such that the heart can carry the increased load placed upon it by the altered circulation.

Some venous blood must be directed into the aorta, for it is the direction of the unoxygenated blood to the lungs which is of benefit to the patient. Indeed, the fundamental difference between the persistent patency of the ductus arteriousus as an isolated malformation and the creation of an artificial ductus in a tetralogy of Fallot is that in the former only fully oxygenated blood flows through the ductus arteriousus to the lungs, whereas in the latter the aorta over-rides the ventricular septum and consequently some venous blood from the right ventricle is directed into the aorta and hence to the lungs for aeration. After operation, the oxygen saturation of the arterial blood rises to between 75 and 85 per cent but it never reaches 100 per cent. Furthermore, in most instances there is a fall in the oxygen saturation of the arterial blood with exercise; consequently, although at rest the oxygen saturation of the blood which is directed through the anastomosis to the lungs may be slightly higher than that of normal mixed venous blood, upon exercise the blood directed to the lungs is closely comparable to that directed to the lungs from the right ventricle in the normal heart.

An over-riding aorta or some other right-to-left shunt is essential for the direction of venous blood to the lungs. The over-riding of the aorta may, in doubtful cases, be determined by a number of methods. The simplest of these is the determination of the circulation time. An abnormally short circulation time, arm-to-tongue, of less than ten seconds is clear indication that venous blood has reached the aorta without passage through the lungs. In doubtful cases angiocardiography may be of great help by the early visualization of the aorta. Catheterization of the heart will also demonstrate the over-riding aorta, if the catheter passes directly from the right ventricle into the aorta.

In one child with a situs inversus and a levocardia, angiocardiograms revealed that a right superior vena cava opened into the right auricle and that a persistent left superior vena cava opened into the left auricle. The aorta arose entirely from the left ventricle. In this instance there was clinical and laboratory evidence of reduced pulmonary blood flow. Inasmuch as venous blood was directed to the aorta by way of the anomalous superior vena cava, it was believed that the patient would be benefited by operation. Such was the case. After operation the oxygen saturation rose from 67 per cent to 78 per cent and the red

blood cell count fell from 10 million to 5.2 million per cubic millimeter. Moreover, there was virtually no demonstrable change in the size of the heart.

The ease with which oxygenated blood from the left ventricle is directed to the aorta is determined by the size of the aorta and the degree of the dextroposition. Usually the aorta arises mainly from the left ventricle and only slightly over-rides the ventricular septum. Unfortunately, there are a few cases in which the aorta over-rides the ventricular septum to such an extent that, after operation, the left ventricle has been unable to expel the increased volume of blood which has been returned from the lungs to that chamber. Under such circumstances angiocardiography is of little aid, because in the presence of pulmonary stenosis so little dye reaches the lungs and the diffusion of the dye through the systemic circulation is so great that it is impossible to visualize the return of the dye to the left side of the heart. Catheterization of the heart gives little or no information concerning the left side of the heart. Consequently, this problem remains an enigma.

If there is a single ventricle, there is never any difficulty in the expulsion of the blood from the common chamber into the aorta. Furthermore, there will be complete admixture of oxygenated blood from the left auricle and venous blood from the right auricle in the common ventricle. In such a malformation the crucial factor is not the structure of the ventricle and its relation to the aorta, but the structure of the tricuspid valve and of the auricular septum and the severity of the pulmonary stenosis. If there is a gross defect in the auricular septum, no difficulty will be encountered in the direction of blood from either auricle to the ventricle. If, however, there is tricuspid atresia and only a small defect in the auricular septum, there may be difficulty in the expulsion of blood from the right auricle to the left.

The expulsion of blood from the right auricle becomes of great importance in cyanotic patients with a left axis deviation. On the basis of a limited number of autopsies, patients with a cardiac contour similar to that of a tetralogy of Fallot but with electrocardiographic evidence of left ventricular hypertrophy frequently have tricuspid atresia and defective development of the right ventricle; often the right ventricle is virtually a blind sac from the base of which the pulmonary artery takes its origin. Under such circumstances, the flow of blood is from the right auricle to the left auricle and thence to the left ventricle and out by way of the aorta. In all such malformations some defect in the auricular septum is inevitable. The defect may, however, be so small that there is difficulty in the expulsion of blood from the right auricle. The presence or absence of pulsations at the margin of the liver offers a valuable clue to the structure of the auricular septum. Pulsation at the margin of a liver of normal size is strong presumptive evidence of tricuspid stenosis or atresia combined with an opening in the auricular septum so small that there is difficulty in the expulsion of blood from the right auricle. In some instances, although before operation the defect in the auricular septum may have been sufficiently large to permit the expulsion of blood from the right auricle, with the increased minute output of the heart after operation this has no longer been possible, and the

patient has developed right-sided cardiac failure with a pulsating liver. Over a period of weeks most of these patients have adjusted to the load and have left the hospital improved; in two infants, however, the strain on the heart ultimately proved fatal.

A single ventricle is also relatively common in patients with persistent cyanosis who have a dextrocardia with or without situs inversus. In such malformations it is usual to find that both the mitral and the tricuspid valves or a common atrioventricular valve open into the common ventricle. Under such circumstances, it is the severity of the pulmonary stenosis which is of importance. It is essential for the pulmonary stenosis to be extreme because, inasmuch as both vessels arise from the same chamber, the stenosis of the pulmonary orifice is the principal mechanism which lowers the pressure in the pulmonary artery. The pulmonic pressure must be appreciably lower than the systemic pressure for blood to flow from the aorta to the lesser circulation. In two instances of a single ventricle in combination with a partial rotation of the heart, although the pulmonary artery was smaller than the aorta, the pulmonary pressure was relatively high; so high that the anastomosis did not continue to function. If, however, there is extreme pulmonary stenosis or pulmonary atresia and provided blood can flow from both auricles into the single ventricle, a single ventricle is quite as amenable to this operation as is a tetralogy of Fallot.

The cardiac reserve and the ability of the heart to adjust to the altered circulation are best demonstrated by the postoperative course.* The amount of cardiac enlargement which has occurred after operation has varied from patient to patient. The operation, however, has rarely led to progressive cardiac enlargement in patients with a tetralogy of Fallot. Indeed, of the first 220 patients operated on for pulmonary stenosis or atresia who were discharged improved, between February, 1945, and July, 1947, only three† are known to have died of cardiac failure. Two of these patients were infants who had electrocardiographic evidence of left axis deviation, in whom the clinical diagnosis was pulmonary atresia combined with tricuspid atresia and single ventricle. In one the diagnosis was confirmed at autopsy. In this instance, the auricular septum had only a small defect; the defect was so small that the heart was unable to maintain compensation after the rate of the circulation had been increased by the operation. The third death from cardiac failure was in a child with a spastic quadriplegia; autopsy was not permitted.

Although there have been only three deaths from cardiac failure, two other patients have developed cardiac failure and, in a number of instances, the operation has led to considerable cardiac enlargement. Great or progressive cardiac

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*Detailed follow-up studies are to be reported by R. Whittemore and H. B. Taussig.

†In addition to these three cases, there have been five other deaths. Three died suddenly. Autopsy was obtained in only one of these patients. In this instance there was an extensive medial sclerosis and a recent myocardial infarction. The second patient died suddenly several weeks after dental extraction; prior to dentistry she had received no prophylactic therapy and died while her jaw was swollen. The third died suddenly while convalescing from jaundice.

During the six-month interval, July, 1947, to December, 1947, two more children have died suddenly. One proved to have an unsuspected streptococcus meningitis and the other a thrombus in the left ventricle.

enlargement is clearly an unfavorable sign and, unless a balance is established, will ultimately cause death.

Fortunately, progressive cardiac enlargement has been rare. Indeed, only two or three patients of these first 220 patients followed for a period of more than two years have been known to continue to show increase in the size of the heart after the sixth postoperative month. It has been gratifying to find that in approximately 40 per cent of patients the operation has caused no demonstrable cardiac enlargement. Quite a number of patients (approximately 30 per cent) have developed cardiac enlargement during the first three weeks after operation but thereafter there has been no further cardiac enlargement. Almost an equal number of patients have shown an increase in the size of the heart between the time of discharge and their return for the six-month checkup; thereafter, the heart has adjusted to its load and there has been no further cardiac enlargement. The initial enlargement is undoubtedly caused by the increased load placed on the heart by the altered circulation. The enlargement which occurs between three weeks and six months after operation coincides with the period during which, for the first time, the patient has greatly increased his acitivity.

The degree of cardiac enlargement has varied from patient to patient. In general, there has been greater cardiac enlargement when the innominate artery has been used for the anastomosis than when the subclavian artery has been used, and the abnormally small hearts have shown greater cardiac enlargement than have the hearts which were at or above the upper limits of normal. Many of these patients with abnormally small hearts had extremely low basal metabolic rates. The operation caused prompt rise in the basal metabolic rate and a corresponding increase in the minute output of the heart. This may explain why many patients with very small hearts, which were associated with a low basal metabolic rate, have shown marked increase in the size of the heart postoperatively. In most of these patients the innominate artery was used for the anastomosis. Thus, a number of factors are involved: the altered circulation, the altered metabolic rate, the increased work demanded of the heart associated with the increased activity of the patient, and the size of the vessel used for the anastomosis. The relative importance of the various factors in the production of cardiac enlargement is under investigation. The objective is to place a minimal strain on the heart and to give adequate, not excessive, pulmonary blood flow.

All present evidence indicates that in the vast majority of instances adequate circulation to the lungs can be attained by the use of the subclavian artery. Table II illustrates how great an effect may be attained upon the oxygen saturation of the arterial blood and the polycythemia three weeks after an operation in which the subclavian artery has been anastomosed to the pulmonary artery. Table III shows the changes in the arterial oxygen saturation, the red blood cell count, and the hematocrit reading before and immediately after operation, and six months, one year, and two years after the anastomosis of the innominate artery to the pulmonary artery. Table IV shows similar determinations in a series of cases in which the subclavian artery was used for the anastomosis.

TABLE II. COMPARISON OF THE OXYGEN SATURATION OF THE ARTERIAL BLOOD, RED BLOOD CELL COUNT, HEMOGLOBIN, AND HEMATOCRIT BEFORE AND AFTER A BLALOCK-TAUSSIG OPERATION (SUBCLAVIAN ANASTOMOSIS)

NAME	OXYGEN SATURATION (%)		RBC (MILLIONS)		HGB. (GMS)		HCT. (MM.)	
	BEFORE OPERATION	AFTER OPERATION	BEFORE OPERATION	AFTER OPERATION	BEFORE OPERATION	AFTER OPERATION	BEFORE OPERATION	AFTER OPERATION
B. W.	56	83	9.7	5.9	29	15	73	47
G. W.	24	64	7.9	6.4	22	17	73	55
H. W.	24	80	7.3	4.7	—	14	64	41
M. F.	29	70	8.7	5.6	19	14	73	50
B. W.	36	82	9.7	5.9	—	—	73	47

TABLE III. THE EFFECT OF A BLALOCK-TAUSSIG OPERATION (INNOMINATE ANASTOMOSIS) ON THE ARTERIAL OXYGEN SATURATION, THE RED BLOOD CELL COUNT, AND THE HEMATOCRIT READING OF FIVE PATIENTS WHO HAVE BEEN FOLLOWED FOR TWO YEARS

	NAME	PRE-OP.	POST-OP.	6 MO.	1 YR.	2 YR.
		Arterial Oxygen Saturation (Per Cent Saturation)				
1	B. R.	36	82	86	84	—
2	J. S.	65.8	79	84	83	68
3	M. C.	20.6	47.9	58.9	59	64
4	J. R.	20.5	67.3	73	64	72
5	J. B.	46	75	79	87	81
		Red Blood Cell Count (Millions)				
1	B. R.	7.6	5.7	4.9	4.3	5.4
2	J. S.	9.0	6.9	5.3	5.0	4.8
3	M. C.	5.7	5.2	6.3	6.3	6.4
4	J. R.	9.1	6.2	5.3	4.8	5.9
5	J. B.	9.6	7.0	5.9	4.3	4.9
		Hematocrit Reading				
1	B. R.	57	46	—	47	48
2	J. S.	71	56	43	47	41
3	M. C.	45	42	48	47	53
4	J. R.	66	53	53	44	51
5	J. B.	84	48	37	42	42

Illustrative cases are given in all tables. In Table III it will be noted in Case 2 that although the last determination of the arterial oxygen saturation has fallen, the red blood cell count and the hematocrit reading have not increased. Therefore, it is hoped that the fall in oxygen saturation of the arterial blood was due to the fact that the patient was crying when the sample was taken. A

TABLE IV. THE EFFECT OF A BLALOCK-TAUSSIG OPERATION (SUBCLAVIAN ANASTOMOSIS) ON THE ARTERIAL OXYGEN SATURATION, THE RED BLOOD CELL COUNT, AND THE HEMATOCRIT READING ON FIVE PATIENTS WITH PULMONARY STENOSIS OR ATRESIA

	NAME	PRE-OP.	POST-OP.	6 MO.	1 YR.	2 YR.
			Arterial Oxygen Saturation (Per Cent Saturation)			
6	R. S.	78	85	86	88	88
7	H. G.	65	81	82	—	83
8	H. O.	59	77	76	—	71
9	M. S.	49	68	78	77	81
10	P. R.	47	67	7	78	76
			Red Blood Cell Count (Millions)			
6	R. S.	6.4	5.5	5.5	5.5	5.5
7	H. G.	10.5	6.6	5.5	5.0	4.8
8	H. O.	6.3	5.6	4.4	6.0	6.1
9	M. S.	6.6	4.7	5.4	5.5	5.3
10	P. R.	9.8	6.6	7.8	5.5	5.5
			Hematocrit Reading			
6	R. S.	59	48	41	46	46
7	H. G.	86	56	47	—	47
8	H. O.	59	49	41	—	51
9	M. S.	64	51	54	54	51
10	P. R.	68	56	58	51	46

similar fall was noted in Case 4 in the sample taken at one year of age. In Case 3, although the oxygen saturation has risen steadily, the red blood cell count has also risen. This patient was an infant. At the time of operation, as so frequently occurs in early infancy, there was no compensatory polycythemia. The arterial oxygen saturation, although it has risen markedly, has only just reached 64 per cent. It is hoped that it may rise still further, and that when it reaches 75 to 80 per cent, the red blood cell count will again decline. Obviously the combination of a red blood cell count of 6 million and an arterial oxygen saturation of 64 per cent is better than that of a red blood cell count of 5 million and an arterial oxygen saturation of 20 per cent.

In Table IV, Case 8, the red blood cell count fell after operation but has subsequently risen to the preoperative level, and the arterial oxygen saturation has fallen slightly. This child had an unusually small subclavian artery and it is possible that the orifice of the anastomosis may not be increasing in size in proportion to the growth of the child. In the future, this child may require another operation. Two infants have already required a second operation.

In addition to these two, two other patients have had a recurrence of cyanosis and one has again developed polycythemia.

The one other unfavorable complication which we have encountered is subacute bacterial endocarditis. One child* has had and has been cured of subacute bacterial endocarditis.

In brief: the follow-up studies indicate that in most children the anastomosis of the subclavian artery to the pulmonary artery has been virtually as beneficial as has the innominate artery and that the load placed on the heart has not been as great. The oxygen saturation of the arterial blood has risen to between 70 per cent and 80 per cent, and the red blood cell count, the level of the available hemoglobin, and the hematocrit reading have returned to normal values. In the vast majority of instances the children have to date maintained this improvement.

SUMMARY

The Blalock-Taussig operation is of benefit to any patient who suffers from lack of adequate pulmonary blood flow, provided the structure of the heart is such that it is able to adjust to the altered circulation.

Experience has shown that a patient with a tetralogy of Fallot can adjust to the altered circulation. The other types of malformation which have been improved by operation are those with a cardiac contour similar to that of a tetralogy of Fallot with left axis deviation, those with partial rotation of the heart on its axis, possibly those with "pure" pulmonary stenosis and an auricular septal defect, and a few with unusual arrhythmias. In atypical cases an effort is made to determine whether the condition is such that the patient can be helped by increasing the circulation to the lungs.

The six criteria essential for successful operation are (1) the primary difficulty must be lack of adequate pulmonary blood flow; (2) there must be a pulmonary artery to which to anastomose the systemic artery; (3) a systemic artery must be available for the anastomosis; (4) the difference in pressure between the systemic and pulmonic circulations must be sufficiently great for blood to flow from the aorta to the lungs; (5) the structure of the lungs must be such that the patient can tolerate the collapse of one lung and the temporary occlusion of one pulmonary artery; and (6) the structure of the heart must be such that it can adjust to the altered circulation. The methods for the determination of each of these factors are discussed.

In an analysis of the structure of the heart it is emphasized that (1) venous blood must be directed to the systemic circulation, (2) the increased volume of oxygenated blood which is returned from the lungs must be able to reach the aorta; (3) the structure of the heart must be such as to permit the continuous circulation of the blood at an accelerated rate; (4) the structure of the heart must also be such that the operation does not cause progressive cardiac enlargement. Each of these factors is analyzed.

The effect of the altered circulation on the size of the heart is discussed in the light of the long-time results of the operation. Less than 5 per cent of the patients have shown progressive cardiac enlargement or died of cardiac failure.

*Since this paper was given seven other children have developed endocarditis. Five have been cured, one is still under treatment, and from one we have no report.

Thirty per cent have shown no increase in heart size. Thirty per cent have shown increase in heart size during the first three weeks after operation and then have adjusted to the load, and 30 per cent have shown cardiac enlargement between the time of discharge and the six-month checkup and thereafter have shown no further increase in heart size.

In general, the results from the use of the subclavian artery, as estimated by the oxygen saturation of the arterial blood, the red blood cell count, and the hemoglobin level, have been as beneficial as when the innominate artery has been used for the anastomosis and, moreover, this former group of patients has shown less increase in the size of the heart.

A child with a tetralogy of . allot has a 90 per cent chance of being greatly improved by the operation and an equally good chance of maintaining that improvement.

CORONARY ARTERY DISEASE IN MEN EIGHTEEN TO THIRTY-NINE YEARS OF AGE

Report of Eight Hundred Sixty-Six Cases, Four Hundred Fifty With Necropsy Examinations*

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INTRODUCTION

PRIOR to World War II, coronary artery disease in men under 30 years of age was regarded as rare, and in men between 30 and 40 years of age, as uncommon. The present report of 866 cases in men between the ages of 18 and 39 years, inclusive, was made possible by the concentration of pathologic material from the Army during the war period at the Army Institute of Pathology and by the centralization of records of disabled veterans at the Veterans Administration Headquarters, both in Washington, D. C. In 450 cases,** the diagnosis was established by necropsy, and in 400 cases,*** the patients survived typical attacks of acute myocardial infarction. Actually 416 cases in the Veterans Administration were studied; but sixteen of these patients**** died subsequently, and although the diagnosis was also verified by necropsy in five, the necropsy records of these cases are not included in this report. Additional cases were still being reported after the series used in this report had been concluded, Sept. 1, 1946. Furthermore, the cases of many living patients were excluded because of inadequate data or atypical features, and many protocols were discarded because of inadequate clinical or pathologic data or insufficient pathologic material for study. The clinical data were considered satisfactory, and the tissues and sections available were sufficient for verification in all fatal cases included

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**Hereafter called "fatal cases."
***Hereafter called the "survivors." These were all men who served in the Army.
****Hereafter called "sixteen additional cases." These were all men who served in the Army.

in this series. Only those cases were accepted in which there was advanced coronary artery sclerosis and no other adequate cause of death. Thirty-seven of the fatal cases were reported before September, 1940, when the National Guard was mobilized; the remainder were accumulated after that date. All of the cases of survival of a typical attack of acute myocardial infarction were observed after Dec. 7, 1941.

REVIEW OF LITERATURE ON CORONARY ARTERY DISEASE IN PERSONS UNDER FORTY YEARS OF AGE

An extensive review of the literature has been made to determine the reported incidence of coronary artery disease in persons under 40 years of age. Several historical facts influence the results. Disease of the coronary arteries has been recognized for many years, but prior to the twentieth century little if any attempt at ante-mortem diagnosis was made, because it was generally regarded as of interest primarily to pathologists. Wolff and White,[1] writing in 1926, ascribed an ante-mortem diagnosis of coronary artery disease to Jenner and Parry in the eighteenth century and stated that the diagnosis was proved at necropsy.

The first description of the clinical picture of occlusion of a coronary artery is generally credited to Obrastzow and Straschesko[2] on the basis of their article which appeared in 1910. In America, Herrick's[3] original contribution on the subject appeared in 1912 and since then has been accorded the place of honor in American writings on coronary artery disease. It is interesting that in this article Herrick referred to two cases occurring in men under 40 years of age. His reference to Chiari's case has not been identified, but the other case, that of Merkel,[4] appears to be an authentic instance of coronary artery occlusion in a man 37 years of age. This case was one of aortic insufficiency, probably of syphilitic origin, in which, in addition to the aortitis, there were marked sclerotic changes in both right and left coronary arteries, the left being completely occluded. Because of the associated pathologic conditions, this case is not included in our tabulation.

The older literature deals largely with the subject of angina pectoris, although without doubt many of the cases were, in fact, coronary artery disease. Huchard,[5] in 1899, presented a large series of cases with briefs from 185 autopsies, most of which he had collected from the literature. In this group there were twenty-nine patients under the age of 40 years. Study of the autopsy briefs leads one to believe that the nature of the disease in many of the cases presented was syphilitic aortitis with secondary involvement of the coronary orifices. A number of others were undoubtedly due to rheumatic valvular lesions. However, careful scrutiny of Huchard's material indicates that nearly one-half of the cases in which the age was less than 40 years may have been instances of coronary artery sclerosis. Since in many of these cases microscopic descriptions are lacking and the data are incomplete, they have not been included in the accompanying tabulation. Mackenzie,[6] in his treatise on angina pectoris, included in an appendix a total of 160 case reports. There are twenty cases involving patients under the age of 40, and four of the twenty appear to be instances of

REPORTS IN LITERATURE OF PATIENTS UNDER FORTY YEARS OF AGE WITH CORONARY ARTERY DISEASE

AUTHORS	NUMBER UNDER 20 YR.	AGE	SEX	NUMBER BETWEEN 20 AND 29 YR.	SEX	TOTAL UNDER 40 YR.	SEX
Dreschfeld[16]	1	12	M			1	M
Wild[17]	1	12	F			1	F
Gilford[18]	1	18	M			1	M
Vaquez[19]	1	18	F			1	F
Benda[20]	1	13	F			1	F
Jamison and Hauser[21]	1	18	M			1	M
Barnes and Ball[22]	1	Under 20	?			?	?
Boas and Donner[23]	1	Between 11 and 20	M			12	M
Meakins and Eakin[24]	1	Under 19	M			7	M (6) F (1)
Sprague and Organ[25]	2	Both 15	M			2	M
May[26]	1	19	?			4	?
Zacks[27]	1	19	M			1	M
Jokl and Greenstein[28]	1	10	M			1	M
Hughes (Osler's)[29]						1	M
Palmer[30]						1	M
Klingmann[31]						1	M
Levine and Tranter[32]						1	M
Wearn[33]						1	M
Nathanson[34]						2	?
Christian[35]						5	?
Krumbhaar and Crowell[36]						1	M
Clark[37]						1	M
Kerr and Larkey[38]						2	M
Allan[39]						1	M
Parkinson and Bedford[40]						4	?
Bramwell[41]						2	M
Conner and Holt[42]						20	?
Root and Graybiel[43]						2	M (1) ? (1)
Levy[44]						2	M (1) F (1)
Smith and Bartels[7]						2	M (1)
Lisa and Ring[45]				1	F	3	F (2) ?
Howard[46]						12	M
Riesman and Harris[47]						1	?
Leary[48]				3	M	10	M (9) F (1)
Coelho[49]						1	M
Rathe[50]						1	F
Horine and Weiss[51]						1	M
Cooley[52]						1	M
Fernando[53]				1	M	1	M
White[8]				4	M	14	M
Appelbaum and Nicholson[54]						3	?
Moritz and Beck[55]						5	?
Cooksey[56]						1	M
Mullins[57]				1	M	24	M (18) F (6)
Wright-Smith[58]				1	M	8	M (1) ? (7)
Master, Jaffe, and Dack[59]						21	M (15) F (6)
Willius[60]						6	M
White, Glendy, and Gustafson[61]				1	F	1	F

REPORTS IN LITERATURE OF PATIENTS UNDER FORTY YEARS OF AGE WITH CORONARY ARTERY DISEASE—CONT'D

AUTHORS	NUMBER UNDER 20 YR.	AGE	SEX	NUMBER BETWEEN 20 AND 29 YR.	SEX	TOTAL UNDER 40 YR.	SEX
Glendy, Levine, and White[62]						100	M (96) F (4)
Bean[63]				2	?	10	?
Benson[64]						1	M
Blaze[65]				1	M	1	M
Durant[9]				1	M	6	M
Franklin[10]						1	M
Sampson and Eliaser[66]						3	M (2) F (1)
Halbersleben[67]				1	F	1	F
Scott[11]				1	M	1	M
Goodson, Jr., and Willius[68]				3	?	30	M (24) F (6)
Ferguson and Lockwood[12]				1	M	1	M
Master, Dack, and Jaffe[69]				10	?	39	?
Jokl and Melzer[70]						2	M
Pollard and Harvill[71]						3	M (2) F (1)
Dawber[72]				1	M	1	M
Macdonald[73]				1	M	1	M
Clawson[74]				4	M	23	M (22) F (1)
Reitman, Greenwood, and Kler[13]				1	M	1	M
Smith, Sauls, and Ballew[75]				1	?	5	?
Garvin[76]						6	?
Miller and Woods[14]				1	M	1	M
Weinstein[77]				6	M	10	M
Shullenberger and Smith[78]						1	M
Master, Jaffe, Dack, and Grishman[79]						2	M (1) F (1)
Levan[80]						2	M
Donoso[81]				1	M	1	M
Nay and Barnes[82]						2	?
Kugel[83]				1	M	1	M
Meesen[84]				78	M	326	M
Tullis[85]				1	M	1	M

Total number patients less than 20 years		14
Males	9	
Females	3	
Sex not stated	2	
Total number patients between 20 and 29 years		128
Males	109	
Females	3	
Sex not stated	16	
Total number patients less than 40 years exclusive of 37 cases believed to be reported twice		744
Males	597	
Females	29	
Sex not stated	118	

sclerotic disease of the coronary arteries in young persons. These twenty cases have also been excluded from this tabulation.

In recent years, a number of reviews of the literature on coronary artery disease in younger individuals have served to focus attention on the subject. In 1932, Smith and Bartels[7] collected twenty cases which they believed to be proved coronary artery thrombosis occurring in patients under 40 years of age. To this group they added two cases of their own. In 1935, White[8] reviewed the literature, and although he did not attempt a tabulation of all cases, he did review much of the writing up to that date. In this same article, White added fourteen cases of patients under 40, including four of patients between the ages of 20 and 29 years. In 1937, Durant[9] briefly reviewed the literature, adding seven cases from his own material. In 1938, Franklin[10] added another case, and in the same year, Scott,[11] reporting the case of a 27-year-old man, reviewed the literature and stated that he had found records of 218 cases of coronary artery disease in patients under 40 years of age. A year later, Ferguson and Lockwood[12] added another case with a further review. In 1942, Reitman, Greenwood, and Kler[13] wrote that they had been able to find reports of 221 cases of coronary artery thrombosis occurring in patients under the age of 40 years. In this group, thirty-four patients were under 30, and four, under 20 years of age. The case presented by these authors was that of a 20-year-old man who had experienced a nonfatal attack. In 1943, Miller and Woods[14] reviewed the subject and added a case of a 22-year-old man who had suffered from coronary artery thrombosis with myocardial infarction. They presented in detail eleven cases from the literature, all of which occurred in patients 30 years of age or younger.

The present survey is intended to bring together these various reports and to add to them such cases as we have been able to collect. In tabulation of material from widely scattered sources, the possibility of duplicate reporting arises, and in an attempt to avoid this, certain series have been omitted when it appeared that the material had already been covered in other reports by the same authors. Even so, it is probable that a few cases may have been reported twice. On the other hand, in deleting several series, we have undoubtedly failed to report several bona fide cases. A second difficulty encountered in a survey such as this is that of language. For many years the literature on disease of the coronary arteries has been predominantly American, and, when to the American contributions are added those from other English-speaking countries, a large portion of the literature is accounted for. Today there is a growing world-wide interest in this subject, and the foreign literature is increasing. Only a small number of reports from the foreign literature have been included in the present review, which admittedly is deficient in this respect.

Notwithstanding the limitations just mentioned, we have been able to collect an imposing number of reports of cases of coronary artery disease occurring in individuals less than 40 years of age. Because much of the terminology in the literature is inexact, with coronary artery occlusion, coronary artery thrombosis, and myocardial infarction often being employed as synonyms, we have used the general term "coronary artery disease," and we have not attempted to separate

the reported cases into the various forms of the disease. We have employed the term to designate all atherosclerotic occlusive disease of the coronary arteries, with or without myocardial infarction.

The following list of seventy-eight references concerns a total of 781 patients less than 40 years of age who suffered from coronary artery disease. Notably omitted is the series of eighty cases of fatal coronary sclerosis reported by French and Dock[15] in 1944, because these cases are included in the main body of this study. It should be noted that Meesen's article[84] published in 1944 was apparently the German experience with coronary artery disease among soldiers in World War II.

Several figures should be subtracted from the totals. The series of Goodson and Willius includes one case previously reported by Smith and Bartels. The series of 100 cases reported by Glendy, Levine, and White undoubtedly includes the fourteen cases previously reported by White in 1935 and the one case reported by White, Glendy, and Gustafson in 1937. It is probable that the twenty-one cases reported by Master, Jaffe, and Dack in 1936 are included in the series reported by the same authors in 1939. Altogether this would make thirty-seven cases to be subtracted from the 781, leaving a total of 744 cases of coronary artery disease reported in individuals less than 40 years of age. The thirty-seven cases which we have subtracted from the total are shown in the list because in several instances they give data on the group of patients 20 to 29 years of age which are lacking in the larger series. The inclusion of these cases does not give rise to duplication in the totals of the 20- to 29-year group, however. The list shows that 128 cases have been reported in this age group. The group of those less than 20 years of age includes fourteen patients, the youngest of whom appears to be a 10-year-old boy whose case was reported by Jokl and Greenstein in 1944.

The sex incidence in the groups reported is of interest. The sex of twelve patients less than 20 years of age was reported; nine were of the male and three of the female sex. Of 112 of the patients 20 to 29 years of age, 109 were men and three were women. Of the 744 less than 40 years of age, the sex was specified in 626 cases, being male in 597 and female in twenty-nine. This would indicate a sex ratio of 95 per cent male to 5 per cent female in the entire group under 40 years of age. The sex ratio in the age group of 20 to 29 years would be 97 per cent male to 3 per cent female, whereas in the group under 20, it would be 75 per cent male to 25 per cent female.

ETIOLOGICAL CONSIDERATIONS

Regarding etiology, many factors were investigated in the series we are reporting. Since so many of the 450 men who died in apparent good health died so suddenly that accurate histories could not be obtained from them, questionnaires were sent to the "nearest of kin." In the cases of the 416 men who survived a typical attack of myocardial infarction in the Army, the histories as obtained from the men themselves were utilized. Control groups were used in both categories.

Because of difficulty in obtaining the addresses of some of the persons to whom it was desired to send questionnaires, the final number sent was 291. Copies of the questionnaire were also sent to 213 families of men who died of gunshot wounds. Of the former, only ninety-four questionnaires were answered and twenty-five came back because of wrong addresses, a return of 35 per cent. Of the 213 control questionnaires, sixty-two were answered and eleven came back because of wrong addresses, a return of 31 per cent. The main reason for the low rate of returns was probably the length of the questionnaire, which covered a wide range of information.

There was significant evidence found for a greater familial tendency toward heart disease among the relatives of the patients with heart disease as compared with the control group: 77 per cent for the former as compared with 53 per cent for the latter. For members of the immediate family, the percentages were 51 and 30, respectively. This difference was even greater between the men who survived an attack of myocardial infarction and a control group of 210 amputees and men hospitalized because of gunshot wounds. Hypertension and/or coronary artery disease occurred in the immediate family of the former in 41 per cent and in the immediate family of the latter in only 13 per cent. Thus, it appears that heredity may be an important factor in the development of coronary artery disease in the age group studied.

Other questions asked related to the type of birth, the condition of the mother during pregnancy, the economic status of the family during the childhood of the man, the number of children in the family, the age when walking began, eating habits, illnesses, smoking and drinking habits, temperament, athletic pursuits, occupational history, education, and marital life. Information from the questionnaires brought out the following comparisons in the two groups:

1. Men in the heart disease group were more likely to have a family history of heart disease.

2. The percentage of men of the heart disease group whose mothers were in good condition during pregnancy was slightly higher.

3. Eighty-one per cent of the men of the heart disease group, as compared with 63 per cent of the control group, were reported to be members of middle class families; the remainder of both groups were from poor families.

4. Relatively twice as many who died from heart disease began to walk before 17 months of age.

5. No important differences were apparent in the eating habits of the men in the two groups.

6. The percentage of patients known to have smoked five or more cigarettes daily was 53 per cent for the heart disease group and 57 per cent for the control group, a minor difference. The percentages of those who smoked more than ten cigarettes were, respectively, 68 and 19 in the two groups, which is more striking, and perhaps a more sensitive measure of the differences between the two groups.

7. The percentage of men who began drinking alcoholic beverages before the age of 20 years was slightly higher for the control group. No excessive drinkers were reported for the control group and only six for the heart disease group. Fifty per cent of the patients with heart disease drank.

8. Patients in the heart disease group were somewhat more likely to display nervous and anxiety traits 50 per cent or more of the time than the men in the control group, the percentages being 26 as compared with 16.

9. Relatively more patients in the group with heart disease had been engaged in light or moderately heavy work before entering the Army than had those in the control group. Only 20 per cent in the former group had held jobs involving heavy work, in contrast to 40 per cent in the latter group.

10. Relatively more patients in the heart disease group than in the control group had histories of "pneumonia and pleurisy" (21 per cent as against 9 per cent), "appendicitis" (17 per cent as against 5 per cent), "high blood pressure" (14 per cent as against 3 per cent), "heart trouble" (9 per cent as against 2 per cent), "kidney trouble" (5 per cent as against 0 per cent), and "leaky valve or murmur" (4 per cent as against 2 per cent). The percentages for the ordinary childhood diseases and others differed little in the two groups.

11. Shortness of breath as a frequent complaint was present in 12 per cent of men in both groups. Pain in the chest was often complained of by 16 per cent of patients in the heart disease group, as compared with 8 per cent of the control group. "Indigestion" was a frequent complaint of 22 per cent of patients in the heart disease group and 11 per cent of those in the control group.

The results of the analysis of the questionnaires are given only because they are of interest; the number of cases in both groups is too small to make them significant. The data obtained directly from 392 men who survived an attack of myocardial infarction and from 210 men suffering from traumatic conditions are of greater significance. Here, as we have already stated, hypertension and/or coronary artery disease was about four times as common in immediate members of the family (father, mother, brothers, and sisters) of the patients with heart disease as in the control group. In regard to the use of tobacco, differences between the two groups were not significant. Twelve per cent of the heart disease group denied the use of tobacco, as against 18 per cent of the control group. The respective percentages for those in the two groups who smoked fewer than twenty cigarettes a day were 17 and 14; between twenty and thirty-nine cigarettes a day, 60 and 62; and more than forty cigarettes a day, 11 and 6 per cent. There was, likewise, no significant difference in the two groups in the use of alcohol: In the heart disease group, 22 per cent denied the use of alcohol, 41 per cent admitted only occasional use of alcohol, 30 per cent admitted moderate use, and 7 per cent admitted heavy use. In the control group, 26 per cent did not use alcohol, 31 per cent drank occasionally, 41 per cent drank moderately, and 3 per cent admitted drinking heavily. The estimated degree of the use of alcohol was based on the opinion of the medical officer who questioned the patient, not on any fixed amount of alcohol consumed.

Age.—Table I gives the distribution of 849 men by age,* both in absolute numbers and percentage by years of age, and as compared with the percentage of men of similar ages in the entire Army. The table shows that sixty-four of the men were between 18 to 24 years of age, inclusive; 139 were 25 to 29 years,

*The exact age of one man was not given, but it was known definitely that he was less than 40 years of age.

inclusive; 266 were 30 to 34 years, inclusive; and 380 were 35 to 39 years of age, inclusive. The number having heart disease per 100,000 soldiers of that age rose sharply with advancing years as shown graphically in Chart I, where it is seen that death from coronary artery disease or myocardial infarction was forty times as common in men 35 to 39 years, inclusive, as in those whose ages were 18 to 24 years, inclusive. Presumably, at the time of induction, all, or at least most, of the 850 men were thought to possess normal cardiovascular systems, because they were accepted for service and, even at the time of death or acute myocardial infarction, were assigned to general Army duty.

TABLE I. AGE DISTRIBUTION OF MEN 18 TO 39 YEARS, INCLUSIVE, WITH CORONARY DISEASE COMPARED WITH THAT OF THE ARMY AND OF VETERANS RECEIVING DISABILITY PENSION AWARDS

AGE (YR.)	MEN WITH CORONARY DISEASE						ENTIRE ARMY* (PER CENT)	DISABLED VETERANS† (PER CENT)
	FATAL CASES		SURVIVORS		TOTAL			
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT		
18	1	0.2	0	0.0	1	0.1	3.7	0.1
19	0	0 0	0	0.0	0	0.0	5.2	1.1
20	2	0.4	5	1.2	7	0.8	6.1	3.3
21	4	0.9	2	0.5	6	0.7	7.6	4.9
22	13	2.9	7	1.8	20	2.4	8.0	5.6
23	12	2.7	4	1.0	16	1.9	8.0	6.9
24	10	2.2	4	1.0	14	1.6.	8.0	7.5
25	15	3.3	7	1.8	22	2.6	7.2	7.1
26	16	3.6	7	1.8	23	2.7	6.6	7.1
27	18	4.0	11	2.8	29	3.4	6.2	6.9
28	11	2.4	12	3.0	23	2.7	5.4	5.8
29	18	4.0	24	6.0	42	5.0	4.8	5.4
30	27	6.0	25	6.2	52	6.1	4.2	4.8
31	21	4.7	17	4.3	38	4.5	3.6	4.7
32	31.	6.9	26	6.5	57	6.7	3.1	4.3
33	29	6.5	25	6.2	54	6.4	3.0	4.1
34	34	7.6	31	7.8	65	7.7	2.4	3.7
35	42	9.4	37	9.2	79	9.3	1.8	3.7
36	36	8.0	45	11.2	81	9.5	1.5	3.4
37	36	8.0	46	11.5	82	9.7	1.3	3.3
38	43	9.6	48	12.0	91	10 7	0.8	3.3
39	30	6.7	17	4.2	47	5.5	0.5	3.0
Total	450‡	100.0	400	100.0	850	100.0	100.0	100.0

*Based on data from War Department AGO Machine Records.

†Data from Veterans Administration, Budget and Statistics Division, on veterans who were receiving disability pension awards as of June 30, 1945.

‡Total includes one patient whose age was not definitely stated but was known to be under 40 years.

The number of men who died of coronary artery disease in relation to the size of the Army is rather small, the average during the war years having been 1.5 per 100,000 men per year. The average age of soldiers 18 to 39 years, inclusive, who died suddenly of coronary artery disease was 32.6 years. This may be com-

pared with the average age of 26.0 years for all men in the Army on Sept. 30, 1945 (a very small percentage of Army personnel was above 39 years of age). It is apparent that the men who died from coronary artery disease represent an older group than the average of the Army. Thus, there was only one death from this cause in soldiers below the age of 20 years, although 9 per cent of the men in the Army were under the age of 20 years. In addition, there was a steady rise in coronary deaths with increasing age, the mortality rate in the age group of thirty-five to thirty-nine years, inclusive, having been 12.2 cases per 100,000 men per year, whereas among the group 20 to 24 years of age, inclusive, the rate was only 0.4 per 100,000 men per year.

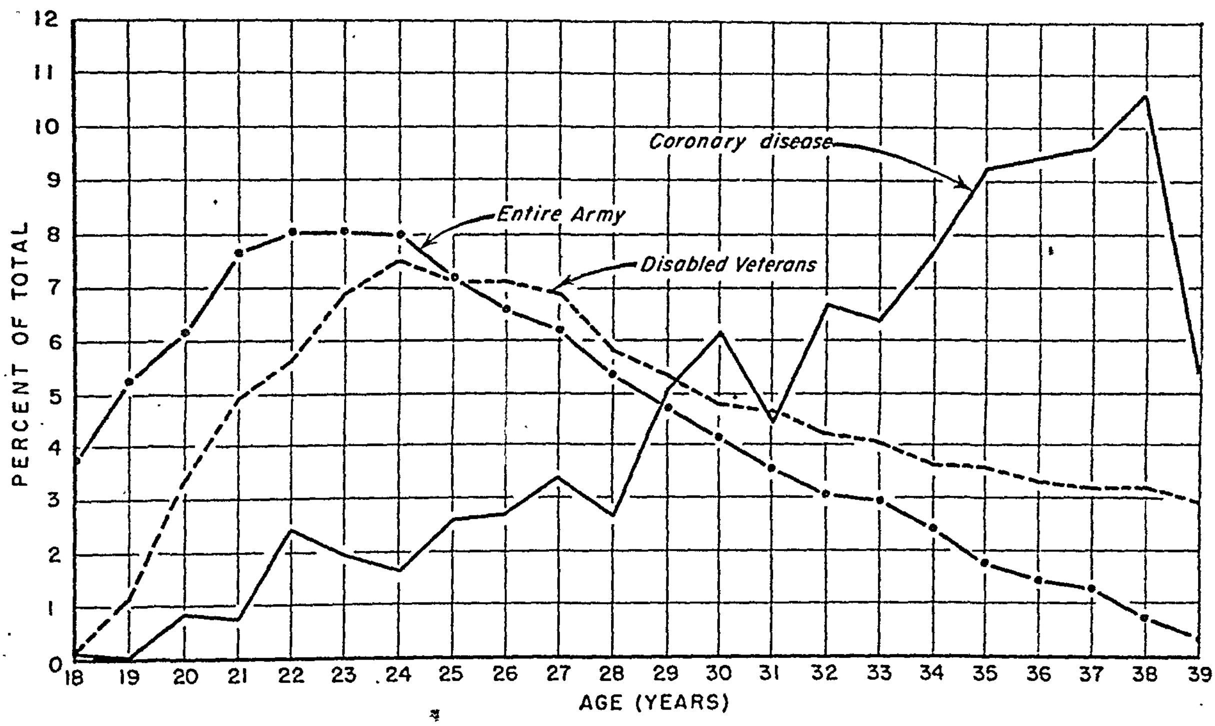

Chart 1.—Age distribution of men 18 to 39 years of age with coronary disease compared with that of the Army and of veterans receiving disability pension awards.

In the group of 400 World War II veterans 20 to 39 years of age, inclusive, who survived an attack of typical acute myocardial infarction, the average age was 33.0 years at the time of the "attack." The average age of the 537,084 veterans of World War II on the service-connected disability rolls as of June 30, 1945, was 29.4 years, with an age range of 16 to 69 years. It may be of interest to note that there were 1,710 veterans less than 40 years of age on the World War II pension rolls as of Dec. 31, 1945, whose disability was diagnosed as the result of coronary artery disease or angina pectoris, and 1,785 veterans 40 to 69 years of age, inclusive, on the pension rolls as of the same date with those diagnoses. The average age of these 3,495 men with coronary artery heart disease was 40.5 years, with an age range of 18 to 67 years.

Between the group of men who died suddenly and those who survived a typical attack of acute myocardial infarction, there is no significant difference with regard to the age factor. There was no indication of any correlation between

the age of the patient and the presence or absence of simple narrowing of the coronary arteries, occlusion (sclerotic alone, thrombotic alone, or both), gross myocardial infarction, or scars of the myocardium in the 450 fatal cases with autopsy.

Race.—There has been considerable discussion in medical literature regarding the incidence of coronary artery disease, acute myocardial infarction, and angina pectoris among Negroes and the differences in the clinical manifestations of the conditions in Caucasians and Negroes. Stone and Vanzant,[86] in a clinical study in 1927, found that arteriosclerotic heart disease was four times as common in white subjects as in Negroes. Schwab and Schultze,[87,88] in 1931 and 1932, arrived at the opinion that it was two and one-half times as common in white subjects. Lisa and Ring,[45] in 1932, found more than four times as many Caucasians as Negroes in 100 cases studied at necropsy. In 1933, Gager and Dunn[89] found twice as many white subjects as Negroes with this disease in a statistical study in Washington, D. C. In a study of necropsy material in the same city in 1935, Hedley[90] came to the conclusion that coronary arteriosclerosis and thrombosis are uncommon among Negroes. Johnston[91] in 1936 found a much greater incidence in white persons. In reports by Bruenn, Turner, and Levy[92] and by Levy and Bruenn,[93] in 1936, the ratio was twelve to one. In Bean's[67] report, in 1937, there were only sixteen Negroes in 300 cases examined at necropsy. Weiss,[94] in 1940, stated that coronary artery occlusion is rare in the Negro in the absence of hypertension. Smith, Sauls, and Ballew,[75] in 1942, reported an incidence of only 0.63 per cent of Negroes with coronary artery occlusion in 2,204 patients of all races with cardiac disease. On the other hand, Holoubek,[95] in 1945, found the ratio of white to Negro patients dying of arteriosclerotic heart disease to be 59 to 41. Fitzgerald and Yater,[96] in 1946, found thirty-five cases of myocardial infarction in Caucasians and the same number in Negroes in the autopsy material for a five-year period at the Gallinger Municipal Hospital, Washington, D. C. In that same period there were twice as many Negroes as white persons hospitalized in that institution, which may indicate that the incidence of myocardial infarction in Negroes is about 50 per cent of that in white persons, the Negroes showing a tendency to die of this disease about a decade earlier in life. Hunter,[97] in 1946, found sixteen Negroes and twenty-six white persons with coronary artery occlusion as the immediate cause of death in a series of 1,000 consecutive autopsies, the Negroes being younger and not suffering the pain so characteristic of the disease in the white race.

Among the 850 men in this series there were 784 Caucasians, 63 Negroes, 1 Filipino, 1 Mexican, and 1 Chinese (Table II). Since only 10 per cent of the men in the Army were Negroes, the incidence of coronary artery disease in the Negroes was somewhat more than two-thirds of that in the white soldiers. The incidence among Negroes was somewhat lower in the group that died than in the group that survived. The average age of the Negroes at the time of death in the fatal series was 32.1 years, and at the time of attack, among those who survived, it was 32.4 years, which clearly indicates that the age factor is not responsible for the somewhat less frequent occurrence of this type of death in Negroes.

TABLE II. RACE DISTRIBUTION OF MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE AND OF ALL MEN IN THE ARMY

RACE	MEN WITH CORONARY DISEASE						ENTIRE ARMY (PER CENT)
	FATAL CASES		SURVIVORS		TOTAL		
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	
White	421	93.5	363	90.7	784	92.2	90.0*
Negro	26	5.8	37	9.3	63	7.4	10.0
Filipino	1				1		
Mexican	1	0.7			1	0.4	
Chinese	1				1		
Total	450	100.0	400	100.0	850	100.0	100.0

*Includes all races other than Negro.

Comparative comment will be made later concerning the clinical and pathologic features of the disease in the Negroes of this group.

Education: The educational level attained by this group is identical with that for all inductees, an average of 9.6 years of completed schooling.

Marital Status: The percentage of married men in this group is consistent with the percentage for all inductees, which was about 25 per cent.

Previous Occupation: The occupations prior to induction of 233 men who died suddenly of coronary artery disease and of the 400 men who survived an attack of acute myocardial infarction, together with a comparison of the distribution of these occupations among all inductees, are shown in Table III. There appears to be a tendency for men with coronary artery disease to have

TABLE III. OCCUPATIONS OF MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE AS COMPARED WITH ALL INDUCTEES

OCCUPATION	MEN WITH CORONARY DISEASE			ALL INDUCTEES (PER CENT)
	FATAL CASES (PER CENT)	SURVIVORS (PER CENT)	TOTAL (PER CENT)	
Factory and labor	42.7	39.8	41.1	59.4
Clerical and sales	21.6	15.2	17.6	13.3
Service except domestic and protective	15.4	25.8	22.1	10.9
Professional and supervisory	9.3	10.8	10.5	4.5
Farm	5.7	5.8	5.8	6.8
Domestic service	2.2	0.5	1.0	4.0
Protective service	1.8	1.5	1.7	0.9
Students	1.3	0.6	0.2	0.2
Total	100.0	100.0	100.0	100.0
Total cases	233	400	633	

been engaged in the less physically arduous occupations, such as clerical, service, professional, and supervisory, as compared with factory, labor, and farm occupations. Thirty-three per cent of the men with heart disease were engaged in service, professional, and supervisory occupations, as compared with 15 per cent of all inductees engaged in such occupations. There seemed to be an unusually large number of men engaged in occupations concerned with the distribution and use of gasoline. This was an impression and is not apparent in the table.

Master, Dack, and Jaffe[98] discussed occupation in relation to coronary artery thrombosis. Of their 555 patients, 49 per cent were laborers, skilled or unskilled, and 51 per cent ran the gamut of other occupations. The authors concluded that occupation was not a factor. From a study of our series, no definite statement can be made, but the figures are at variance with those of these authors.

Height-Weight Factor: French and Dock,[15] in reporting eighty cases which are also included in the group of fatal cases of this series, concluded that overweight was an important etiological factor in these young men. Although our first impression was similar, when we compared the weights of the men in the "coronary" series with a group of 297 men of the same age group who died as the result of accidents, we found that there was no significant difference. Furthermore, a comparison of the weights at induction of 233 of the men who died as the result of coronary artery disease with those of all inductees of the same age group failed to bring out any significant difference. The men, on the whole, gained weight during their Army careers; and, although it is true that most of those who died of coronary artery disease were overweight in comparison with all inductees, they were no heavier than others who had been in Army service for a time but who did not have coronary artery disease (Table IV and Chart 2).

TABLE IV. DISTRIBUTION OF HEIGHT AND WEIGHT IN FATAL CASES OF CORONARY DISEASE AS COMPARED WITH ALL INDUCTEES AND 297 MEN OF SAME AGE GROUP DEAD OF ACCIDENTS*

HEIGHT-WEIGHT GROUP	AT INDUCTION		AT TIME OF DEATH	
	CORONARY DISEASE PATIENTS (PER CENT)	ALL INDUCTEES (PER CENT)	CORONARY DISEASE PATIENTS (PER CENT)	DEATHS FROM ACCIDENTS (PER CENT)
Markedly underweight	14.2	12.5	4.8	3.5
Underweight	19.7	25.0	9.8	10.5
Normal weight	22.7	25.0	21.0	23.0
Overweight	28.8	25.0	43.4	42.6
Markedly overweight	14.6	12.5	21.0	20.4
Total	100.0	100.0	100.0	100.0
Number of cases	233			

*All data based on men 18 to 39 years of age, inclusive.

TABLE V. HEIGHT AND WEIGHT OF MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE COMPARED WITH ALL INDUCTEES

WEIGHT-HEIGHT GROUP*	MEN WITH CORONARY DISEASE			ALL INDUCTEES (PER CENT)
	FATAL CASES (PER CENT)	*SURVIVORS* (PER CENT)	*TOTAL* (PER CENT)	
Markedly underweight	14.2	11.3	12.7	12.5
Underweight	19.7	20.7	20.5	25.0
Normal weight	22.7	17.8	20.1	25.0
Overweight	28.8	27.0	27.6	25.0
Markedly overweight	14.6	23.2	19.1	12.5
Total	100.0	100.0	100.0	100.0

*Classification of weight in relation to height based on measurements at induction.

In making these comparisons of heights and weights as of the time of death, it must be admitted that the data determined at autopsy are inexact. However, for purposes of this study, in which the weights of the control group were obtained in the same manner, there is no reason to presume that one set of data is biased as compared with the other. The more important figures were those obtained at the time of induction, which were accurately determined.

The heights and weights at the time of induction of the 416 men who survived an attack of acute myocardial infarction are compared in Table V with the same data from 233 of the fatal cases and of all inductees. It is noted that

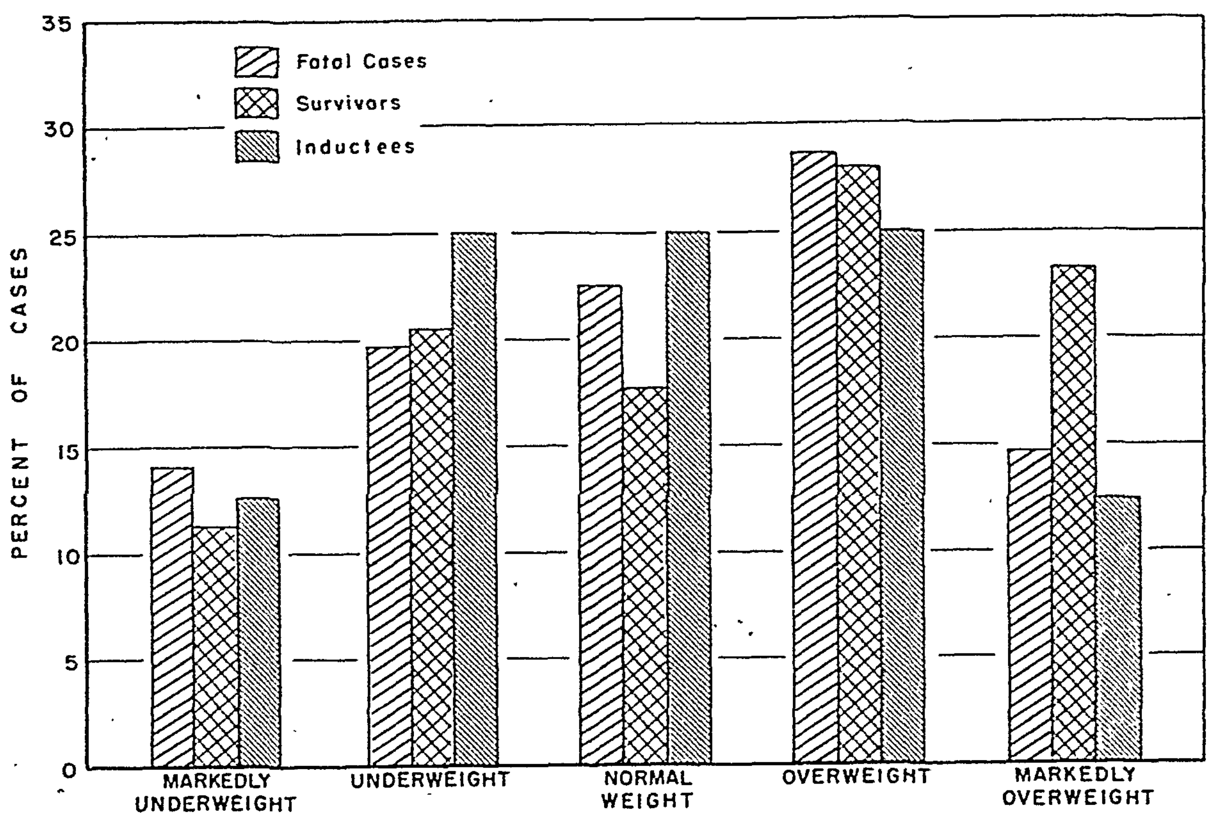

Chart 2.—Height and weight of men 18 to 39 years of age with coronary disease compared with all inductees.

the proportion of markedly overweight men was about 60 per cent greater among the survivors than in the fatal group and about 86 per cent greater among the survivors than for all inductees. The table shows that there is a slight tendency for men with coronary artery disease to be overweight at the time of induction, particularly the survivors of the acute attack, with the deceased patients appearing to be more representative of the Army as a whole.

The standard of reference used for the men at the time of induction was compiled by the Surgeon General's Office from height and weight data collected on 101,142 men at induction stations in January and May of 1943. The definition of obesity is of necessity an arbitrary one. For the purpose of this study, the following height-weight classes were established.

1. The lowest 12.5 per cent of the standard weight distribution for a given height and weight is defined to contain those men markedly underweight.
2. The next 25 per cent is defined to contain those who are underweight.
3. The middle 25 per cent of the standard distribution is defined to contain men who are of normal weight.
4. The next 25 per cent of the standard distribution is defined to contain men who are overweight.
5. The top 12.5 per cent of the standard distribution is defined to contain men who are markedly overweight.

Blood Pressure: The relation between coronary artery disease and blood pressure has been discussed in the literature on heart disease many times. For example, it has been stated that "high blood pressure is more frequently associated with beginning cardiovascular disease than any other discernible sign."[39] It is, therefore, of interest to study this younger group for hypertensive tendencies at the time of induction in order to determine whether there are any indications of prognostic value in blood pressures which might have foreshadowed their death or an attack of myocardial infarction.

Induction blood pressure values were available for 205 patients who died unexpectedly and for 337 patients who survived an attack of acute myocardial infarction. The determinations of the induction blood pressures were made hurriedly and under abnormal conditions. To obtain controlled comparisons, it was desirable to have a group of men whose pressures were taken under the same or similar conditions, and who have, as yet, demonstrated no overt evidence of cardiac disease. As a control group, 210 amputees and other wounded patients, whose records were available through the Veterans Administration, were chosen.

A classification based on the height of blood pressure in millimeters of mercury was arbitrarily established for the analysis:

Normal	110/70 to 139/89	Slightly elevated	140/90 to 159/104
Low normal	100/60 to 109/69	Moderately elevated	160/105 to 199/119
Low	70/50 to 99/59	High	200/120 to 224/129
Very low—under	70/50	Very high	225/130 and above

By classification on this basis of the 205 patients who died suddenly of coronary artery disease and whose induction blood pressures were known and of the control group, the distribution of induction pressures shown in Table VI was

obtained. A slight though definite tendency toward hypertension is evidenced by the patients with coronary artery disease, with 20 per cent of them having had induction pressures above normal as against 5 per cent of the control group. Conversely, 4 per cent of the group with coronary artery disease had pressures below normal as compared with 14 per cent of the control group.

TABLE VI. INDUCTION BLOOD PRESSURES OF MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH FATAL CORONARY DISEASE AND OF ARMY CONTROL GROUP

BLOOD PRESSURE CLASSIFICATION	MEN WITH FATAL CORONARY DISEASE		ARMY CONTROL GROUP	
	NUMBER	PER CENT	NUMBER	PER CENT
Low			1 } 29	13.6
Low normal	8	3.9	28 }	
Normal	156	76.1	173	81.2
Slightly elevated	39	19.0	11	5.2
Moderately elevated	2	1.0		
Total	205	100.0	213	100.0

The systolic and diastolic components of the induction pressures of the fatal cases and the survivors were analyzed separately. In addition to the control group of amputees, the patients with coronary artery disease were compared with a large series presented by Alvarez and Stanley,[100] based upon 1,067 white prisoners between the ages of 25 and 29, and another by Robinson and Brucer,[101] based upon 4,039 men between the ages of 20 and 39 years. The Alvarez-Stanley series gave results which were so similar to the Robinson-Brucer series that, for purposes of simplification, only the former series will be utilized in the following discussion.

The Alvarez-Stanley series contained proportionately more patients with lower systolic pressures than either the amputee group or those of this series. However, patients with coronary artery disease showed significantly greater tendencies toward hypertension than either of the other two groups. As shown in Table VII, only 16 per cent of patients with coronary artery disease had systolic pressures under 120 mm. Hg as compared with 42 per cent for the amputee group and 60 per cent for the Alvarez-Stanley series. Similarly, 28 per cent of the group with coronary artery disease had systolic readings above 139 mm. as against 9 per cent for the amputees and 5 per cent for the Alvarez-Stanley series.

The relative incidence of the systolic pressures may be calculated as follows from Table VII, if one assumes that the amputee blood pressure readings are representative of the Army as a whole.

SYSTOLIC PRESSURE (MM. HG)	CORONARY PATIENTS (PER CENT)	ARMY CONTROL (PER CENT)	RELATIVE INCIDENCE (RATIO)
100 to 119	16.4	41.8	0.39
120 to 139	55.7	49.3	1.13
140 to 169	27.9	8.9	3.13

Thus, it will be seen that of the men with coronary disease there were only 39 per cent as many with systolic pressures under 120 mm. Hg as are normally found in the Army, and over three times as many with pressures above 140 mm. of mercury. The relative incidence of coronary disease is more than twice as great in patients with pressures of 140 to 169 mm. Hg as in those with pressures of 100 to 139 mm. of mercury.

TABLE VII. SYSTOLIC BLOOD PRESSURES OF MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE AND OF ARMY CONTROL GROUP AND ALVAREZ-STANLEY SERIES

INTERVAL (MM. HG)	PER CENT DISTRIBUTION				
	MEN WITH CORONARY DISEASE*			ARMY CONTROL GROUP†	ALVAREZ-STANLEY SERIES
	FATAL CASES	SURVIVORS	TOTAL		
80-89	—	—	—	—	0.6
90-99	—	—	—	—	5.6
100-109	5.9	3.0	4.5	12.7	22.7
110-119	10.7	13.1	11.9	29.1	31 0
120-129	32.8	23.7	28.2	30.5	23.5
130-139	27.8	27.3	27.5	18.8	11 2
140-149	19.0	25.5	22.2	8.9	3.8
150-159	2.9	6.2	4.6	—	1 2
160-169	0.9	1.2	1.1	—	0.4
Total	100.0	100 0	100.0	100.0	100.0
Number of cases	205	337	542	213	4,507

*Pressure taken at induction into Army.

†Composed of amputee patients of the Veterans Administration who showed no signs of cardiovascular involvement.

Essentially the same trend is apparent when the diastolic blood pressures of the patients with coronary disease are compared with those of the control groups. However, it is important to note, in view of the fact that the diastolic pressure is the more significant with regard to the hypertensive trend, that the differences between the groups are somewhat more. Thus, in Table VIII the group with coronary artery disease had 19 per cent with diastolic pressures above 89 mm. Hg compared with 4 per cent for the amputee patients and 5 per cent for the Alvarez-Stanley series.

An analysis of relative incidence for the diastolic pressures similar to that for the systolic pressures yields the following results:

DIASTOLIC PRESSURE (MM. HG)	CORONARY PATIENTS (PER CENT)	ARMY CONTROL (PER CENT)	RELATIVE INCIDENCE (RATIO)
40 to 69	4.8	19.2	0.25
70 to 89	76.1	77.0	0.99
90 to 129	19.1	3.8	5.03

TABLE VIII. DIASTOLIC BLOOD PRESSURES OF MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE AND OF ARMY CONTROL GROUP AND ALVAREZ-STANLEY SERIES

INTERVAL (MM. HG)	PER CENT DISTRIBUTION				
	MEN WITH CORONARY DISEASE*			ARMY CONTROL GROUP†	ALVAREZ-STANLEY SERIES
	FATAL CASES	SURVIVORS	TOTAL		
40-49	——	——	——	——	2.4
50-59	——	0.3	0.1	1.4	11.8
60-69	5.9	3.6	4.7	17.8	27.1
70-79	36.6	19.8	28.3	44.6	38.7
80-89	46.2	49.3	47.8	32.4	14.7
90-99	9.8	24.6	17.2	3.8	5.0
100-109	1.5	1.8	1.6	——	0.3
110-119	——	0.3	0.2	——	——
120-129	——	0.3	0.1	——	——
Total	100.0	100.0	100.0	100.0	100.0
Number cases	205	337	542	213	4,507

*Pressures were taken at induction into the Army.
†Composed of amputee patients of the Veterans Administration who show no signs of cardiovascular involvement.

Thus, among the patients with coronary artery disease there was but 25 per cent of the normal proportion of men with diastolic pressures under 70 mm. Hg and nearly four times as many as are expected to have diastolic pressures over 89 mm. of mercury. There were, consequently, more than four times as many "coronary deaths" in those having diastolic pressures over 89 mm. Hg at induction as there were among those with diastolic pressures under 90 mm. Hg, relative to the number of persons in each group.

Since at the time of induction 28 per cent of the patients with coronary artery disease had systolic pressures between 140 and 170 mm. Hg and 19 per cent of them had diastolic pressures between 90 and 110 mm. Hg, there is a definite, though moderate, trend toward hypertension in this series. The actual number of patients with definite hypertension, however, is small. It must be pointed out that there is an unknown number of men in this age group who were barred from military service because of hypertension, some of whom may now have coronary artery disease and may later die because of it before they reach the age which limits this series. Therefore, the role of hypertension in relation to coronary artery disease in this age group cannot be accurately determined.

The differences in the per cent distributions of blood pressure, either systolic or diastolic, between the patients who died suddenly of coronary artery disease and those who survived an attack of acute myocardial infarction are much less marked than the differences between the patients and either control series. However, it is of interest to note that the pressures of the surviving patients are higher than those of the patients who died. This may be indicative of a greater ability of members of the former group to adjust to their circulatory needs.

The relationship of hypertension to coronary artery sclerosis and acute coronary artery occlusion has been discussed frequently in the literature. Levine and Brown[102] found that 40 per cent of 145 patients were definitely known to have pressures of 160/100 or more before their attack of coronary thrombosis, but many patients who had a normal blood pressure after the attack showed evidence of pre-existing hypertension in the ocular fundi. Sixty-eight and three-tenths per cent of their patients were between 50 and 69 years of age, and only three were under 40 years of age. Hypertension was present in 33.9 per cent of Connor's[103] 274 cases, with the highest incidence in the age group of 56 to 60 years. Allen[104] reviewed several articles on the relation of hypertension to angina pectoris and coronary occlusion and found that the percentages of cases with occlusion in which hypertension occurred varied from 26 to 59. Of the author's 140 patients with occlusion, 73 per cent had hypertension. Palmer[105] found an incidence of 73 per cent hypertension among 212 cases; hypertension was found in only 37 per cent of patients under 50 years of age at the time of the attack and in 78 to 84 per cent in the sixth, seventh, and eighth decades of life. The average blood pressure before the attack was 170/100. In the follow-up it was found that hypertension developed in more than one-half of the cases within one year after the attack; the incidence increased year by year and finally reached 72 per cent. The pressure failed to return to previous levels in one-half of the nonhypertensive cases and in one-third of the hypertensive cases; in one-third of the hypertensive cases the blood pressure remained permanently normal. Master, Dack, and Jaffe[69] found that 62.4 per cent of 500 patients with myocardial infarction had blood pressures of 150/90 or more and that the frequency of hypertension rose directly with age; for instance, only 28 per cent of the men 25 to 34 years of age had hypertension, whereas it was present in 80 per cent of those 75 years of age or older. Gross and Engelberg[106] found the incidence of hypertension in 100 cases of coronary thrombosis to be 90 per cent. The subsequent blood pressure in hypertensive cases following coronary occlusion had no effect on longevity or on the occurrence or the severity and duration of heart failure. However, Bland and White[107] in a series of 200 cases found that during the first few years following the attack, the hypertension of more than 150/100, which existed in 31 per cent of the patients, had no particular effect, but that the added burden of hypertension greatly increased the mortality over a ten-year period (from 2.6 per cent to 13.2 per cent). Rathe[108] found hypertension in 63 per cent of 274 patients prior to the first attack, and a family history of hypertension, cerebrovascular accident, or cardiovascular disease in 48 per cent of the cases. Of the 202 cases of Master, Dack, and Jaffe[109] hypertension was present in 60.4 per cent before the attack but in only 37 per cent after the attack. The hypertension did not influence the frequency of subsequent attacks of occlusion, but did increase the incidence of heart failure, as in the series of Bland and White. Master, Jaffe, Dack, and Silver[110] found previous hypertension in 69 per cent of 538 patients with coronary occlusion; hypertension was more frequent with multiple than with initial attacks of occlusion. Again they emphasized the increase in the incidence of hypertension with age. In one-third of the cases the blood pressure persisted at a low level throughout the hospital stay, whether

the patient had had hypertension previously or not; in one-third there was a gradual return to the initial levels but not to the high levels preceding the attack.

Chambers[111] found the incidence of hypertension in 100 cases of coronary occlusion with myocardial infarction to be 74 per cent. Of thirty-four patients who died of the acute episode, 71 per cent had hypertension. Over one-half of the patients with hypertension gave a history of angina, dyspnea, or decompensation. Chambers concluded that there was no relation between antecedent hypertension and the mortality rate, but that in the group of hypertensive patients the mortality depended directly upon the degree of hypertension. All of the articles quoted included both male and female patients.

Thus, it appears that there is some relationship between coronary artery disease and hypertension which increases with age. It may be that there is an hereditary predisposition to the two diseases or that there is a common etiological factor. Another possibility is that reduction in the coronary blood flow resulting from disease of the coronary arteries may cause hypertension as a compensatory mechanism to increase the head of pressure in the coronary arterial tree.

PRECIPITATING FACTORS

It is probable, of course, that the coronary artery disease in our patients existed at the time of induction. However, the many possible causes for precipitation of the coronary insufficiency or the thrombosis which brought about the terminal event were investigated.

Type of Service.—It was thought that the type of Army service might have had some influence. The Arms or Services regarded as involving normal activity were listed as Medical Corps, Signal Corps, Finance Department, Military Intelligence, and Adjutant General's Office. Those considered to involve heavy or strenuous activity were Infantry, Air Corps, Ordinance, Artillery, Quartermaster Corps, Armored Forces, and Engineers. It was realized, however, that the Arm or Service in which a man was employed did not permit a very accurate estimate of his duties. Table IX gives an analysis by Arm or Service of 295 of the men who died suddenly. There is no significant evidence to the effect that the Arm or Service affected the rate of death from coronary disease. The proportion of cases within each Arm was about equal to the strength of that Arm, with the single exception of the Artillery in which the incidence of coronary artery disease was 3.4 times the percentage strength of the Arm.

An analysis was also made of the number of men by five-year age groups in the two divisions of Arms or Services. There is no indication that age bears any relation to Arm or Service in determining the occurrence of death from coronary artery disease.

Length of Service.—Table X gives the percentages relating to length of service for 709 men classified according to death or survival from the acute attack. Forty per cent of the men died within one year of entering service. Although there are no accurate data available on length of service for the entire Army, it is probable that the preponderance of men in the Army, perhaps as

TABLE IX. DISTRIBUTION BY ARM OR SERVICE OF 295 FATAL CASES OF CORONARY DISEASE IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE

ARM OF SERVICE	DEATHS FROM CORONARY DISEASE		ENTIRE ARMY (PER CENT)
	NUMBER	PER CENT	
Normal Activity Branches	88	29.8	26.3
Medical Department	23	7.8	5.7
Signal Corps	15	5.1	9.0
Others*	50	16.9	11.6
Heavy Activity Branches	207	70.2	73.7
Infantry	46	15.6	22.7
Air Corps	50	17.0	21.5
Ordinance	11	3.7	7.0
Artillery	38	12.9	3.8
Quartermaster	25	8.5	10.0
Armored Forces	13	4.4	2.5
Engineers	24	8.1	6.2
Total	295	100.0	100.0

*"Others" includes Arms or Services such as Finance Department, Military Intelligence, Adjutant General's Office, and so forth.

much as 98 per cent, had more than one year of service. There is every indication, therefore, that those who suffered an acute attack of coronary insufficiency or myocardial infarction tended to have much less service than the men in the Army as a whole, and that the rigors of military service may have been a factor in precipitating death. Also, in general, if the acute attack was fatal, it occurred earlier in the military career than infarction followed by survival. Thus, 45 per cent of deaths from the acute attack occurred during the first year of service, as compared with 34 per cent of the attacks of acute myocardial infarction which the patients survived.

TABLE X. LENGTH OF ARMY SERVICE PRIOR TO ACUTE ATTACK AMONG MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE

LENGTH OF SERVICE UNTIL ACUTE ATTACK (MONTHS)	FATAL CASES		SURVIVORS		TOTAL	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
0-6	80	25.9	63	15.7	143	20.1
7-12	60	19.4	73	18.3	133	18.8
13-35	113	36.6	214	53.5	327	46.1
36-71	26	8.4	46	11.5	72	10.2
72-120	4	1.3	1	0.2	5	0.7
Over 120	26	8.4	3	0.8	29	4.1
Unknown	141				141	
Total	450	100.0	400	100.0	850	100.0

The relationship of age to length of service of 279 of the men who died suddenly and the 400 men who survived an attack of acute myocardial infarction was investigated (Table XI). There appeared to be a definite tendency for the older men to die earlier in their Army careers. Only 24 per cent of the men in the 18 to 24-year age group died during the first year, in comparison with 48 per cent of the 25 to 29 year age group, 49 per cent of the 30 to 34-year age group, and 59 per cent of the 35 to 39-year age group. Among the survivors this trend did not exist in the first year of service, but did appear after that time, following the pattern noted in the men who died.

TABLE XI. AGE IN RELATION TO LENGTH OF SERVICE OF MEN 18 TO 39 YEARS OF AGE WITH CORONARY DISEASE; FATAL CASES AND SURVIVORS WITH LESS THAN SIX YEARS OF SERVICE

LENGTH OF SERVICE (MONTHS)	AGE GROUP								TOTAL 18 TO 39 YEARS	
	18 TO 24 YEARS		25 TO 29 YEARS		30 TO 34 YEARS		35 TO 39 YEARS			
	DIED (PER CENT)	SURVIVED (PER CENT)	DIED (PER CENT)	SURVIVED (PER CENT)	DIED (PER CENT)	SURVIVED (PER CENT)	DIED (PER CENT)	SURVIVED (PER CENT)	NUMBER	PER-CENT
0-6	6.9	17.4	28.2	14.8	31.5	15.0	32.1	16.6	146	21.2
7-12	17.2	21.7	19.6	14.8	17.4	18.9	26.8	20.0	137	19.8
13-35	62.1	43.5	43.5	49.1	43.5	53.3	31.3	56.1	333	48.3
36-71	13.8	17.4	8.7	21.3	7.6	12.8	9.8	7.3	74	10.7
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	690	100.0

Time of Year and Place of Death.—When the months of the year in which deaths occurred were analyzed (Table XII), it was found that the probability of death from coronary artery disease or myocardial infarction was fairly evenly distributed by months throughout the year. This was true whether the soldier died suddenly in his acute attack or survived.

Analysis was also made of 235 of the acutely fatal cases as to incidence of deaths in each of four geographic areas: Northeast and North Central, Southeast and South Central, Middle West and Central, and Far West and Northwest (Table XIII). No statistically significant differences existed between the proportion of deaths in the different geographic areas in relation to the number of men stationed in them.

A further analysis was undertaken to determine whether there were seasonal variations in the distribution of deaths within each of the geographical areas. Although the differences were not statistically significant, there was a slight perponderance of deaths during the summer in the Southeast and South Central area. Such data do not take into account, however, the effect of lack of acclimatization, which would be difficult to assay.

These data are at variance with those of most writers on the effect of climate or season (Wolff and White,[1] Wood and Hedley,[112] Mullins,[57] Bean,[63] and Bean

TABLE XII. MONTH OF OCCURRENCE OF ACUTE ATTACK OF CORONARY DISEASE AMONG MEN 18 TO 39 YEARS OF AGE

MONTH	FATAL CASES		SURVIVORS		TOTAL	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
January	27	6.8	40	10.0	67	8.4
February	32	8.0	32	8.0	64	8.0
March	36	9.0	39	9.8	75	9.4
April	27	6.8	38	9.5	65	8.1
May	31	7.8	34	8.5	65	8.1
June	29	7.2	44	11.0	73	9.1
July	33	8.3	34	8.5	67	8.4
August	42	10.5	27	6.8	69	8.6
September	39	9.8	34	8.5	73	9.1
October	41	10.3	29	7.2	70	8.8
November	33	8.3	23	5 7	56	7.0
December	29	7.2	26	6.5	55	7.0
Unknown	51				51	
Total	450	100.0	400	100.0	850	100.0

TABLE XIII. GEOGRAPHIC DISTRIBUTION AT TIME OF DEATH OF MEN 18 TO 39 YEARS OF AGE WITH CORONARY DISEASE

SECTION OF UNITED STATES	DEATHS FROM CORONARY DISEASE		DISTRIBUTION OF ENTIRE ARMY (PER CENT)
	NUMBER	PER CENT	
Northeast and North Central	72	30.6	27.5
Southeast and South Central	93	39.6	46.7
Middle West	48	20.4	18.5
Far West and Northwest	22	9.4	7.3
Total	235	100.0	100.0

and Mills,[113]) who concluded that attacks of acute coronary artery occlusion are definitely more frequent in winter than in summer, especially in north temperate regions. Master, Dack, and Jaffe,[98] noted a higher incidence in December and January for 612 patients, but they did not believe that season was important in determining the incidence of acute attacks.

Activity When Stricken.—There has been considerable contention regarding the effect of activity in inaugurating a "coronary attack," that is, fatal coronary insufficiency (sometimes called fatal angina) or myocardial infarction. Luten,[114] in 1931, expressed the opinion that coronary artery occlusion occurs most commonly during sleep because of lowering of diastolic pressure and lessening of systolic output. On the other hand, Green and Burton,[115] in 1933, concluded from a study of 100 cases that unusual activity or stress or marked departure from ordinary habits of living preceded fatal angina or coronary artery throm-

bosis more often than not, and that many of these departures were preventable. De Santo,[116] in 1935, reported a small group of cases in which operations or violent trauma resulted in arterial occlusion in sclerotic vessels and suggested that occlusion often occurs during or immediately after anesthesia when consciousness is absent or dulled. In 1936, Phipps[117] in a study of 437 cases noted that physical stress appeared to be related to the onset of the attack in 23 per cent, but that in 8 per cent it occurred during sleep, and in the majority of cases, during rest or mild or unusual physical exertion. Bean[63] (1937), in a study based on 300 autopsies selected from 9,626 consecutive protocols, found that in forty-four cases of infarction the onset of symptoms occurred while the patients were at rest, sixteen of them being asleep; in forty-four, during activity; in fourteen, while the patients were eating; and in four, while the patients were deeply intoxicated. In a study of 817 attacks or coronary artery thrombosis occurring in 555 patients, Master, Dack, and Jaffe[98] (1937) found that 21.7 per cent occurred while the patient was at rest, 19.6 per cent while he was asleep, 13.6 per cent during mild activity, 5.3 per cent during moderate activity, and 18 per cent while the patient was walking; thus, 41.3 per cent occurred while the patient was at rest or sleeping and 36.9 per cent during mild or moderate activity. In only 2.1 per cent was there a history of unusual or severe exertion. These authors concluded that there is no one factor or group of factors responsible for the onset of an attack of coronary artery thrombosis and that the apparent association of an attack with some external condition is merely coincidental. In another article[118] the same authors arrived at the same conclusion and added that 4.1 per cent of attacks occurred following surgical operations, a circumstance they considered to be significant. Later, in 1941, Master, Dack, and Jaffe[119] studied the precipitating factors of the premonitory symptoms of coronary artery occlusion in seventy cases and concluded that effort did not initiate them any more than it did those in the case of complete occlusion. However, in 1944, Master,[120] in defining angina pectoris, acute coronary insufficiency, and coronary occlusion, expressed the opinion that acute coronary insufficiency is associated with a precipitating factor which might be either an increased demand for coronary blood flow or anything which actually reduced the flow.

Paterson,[121] in 1939, pointed out that hours or days might elapse between the time of inception of a thrombus in a coronary artery and the moment when occlusion, with its resulting cardiac pain, occurred, and that, therefore, the activity of the patient at the time when symptoms arose did not necessarily solve the problem as to whether activity had any effect in the production of coronary artery occlusion. He considered rupture of intimal capillaries a prime factor in precipitating thrombotic occlusion and was of the opinion that exertion or emotional stress might easily increase the pressure in a capillary of an atheromatous plaque to the point of rupture. Softening of atheromatous tissues surrounding and supporting the capillary walls would still further increase the likelihood of rupture under such conditions.

Boas,[122] in 1939, also stated that trauma to intimal capillaries, either by nonpenetrating thoracic injuries or unusual effort, was in some instances the cause of subintimal hemorrhages which resulted in thrombosis.

Smith, Sauls, and Ballew,[75] in 1942, discussed the events associated with the immediate "attack" in fifty-three of 100 cases of coronary occlusion. In thirty-two, physical exertion was associated with the attack; in ten, bed rest; in five, a heavy meal; in four, a severe emotional upset; and in two, a major operation. In 1941, Blumgart, Schlesinger, and Zoll[123] concluded that shock, no matter how produced, in elderly patients, particularly those showing evidence of arteriosclerosis, may lead to the development, not only of single, but often of multiple fresh coronary arterial occlusions as well. Later (1945), Blumgart[124] attacked the thesis that unusual exertion does not play a precipitating role in certain cases. He pointed out that other factors in addition to effort and emotional stress, such as fatigue, exposure, cold, and eating, place an increased burden of work on the heart. He was interested also in the occurrence of myocardial infarction without coronary artery occlusion, which he thought could be due to relative ischemia. He concluded that subintimal hemorrhage or rupture of an atheromatous abscess could easily be influenced by undue exertion or strain.

Meesen,[84] in 1944, however, was unable to ascribe a causal effect to activity at the time of sudden death of 115 soldiers. He stressed, on the other hand, that there seemed often to be a preceding infection of a respiratory nature.

There was a fairly accurate account of the activity of 324 of the 450 men in the Army series who died and of 363 of the veterans who survived an attack of myocardial infarction. The categories of sleeping, in bed but awake, mild activity, moderate activity, and strenuous activity were established. Mild activity referred to sedentary occupations; moderate activity, to occupations involving ordinary walking; and strenuous activity, to drilling, marching, running, laboring, and participation in sports. Mild and moderate activity, being ordinary or usual, may be grouped together in the final analysis of the effect of activity. Consideration should also be given to the average amount of time spent daily in the various activities. Table XIV gives the numbers and percentages of the two groups of men engaged in the various activities when stricken and the estimated number of hours and percentages spent daily in the different types of

TABLE XIV. ACTIVITY AT ONSET OF ACUTE ATTACK OF MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE

ACTIVITY	FATAL CASES		SURVIVORS		TOTAL		ESTIMATED AMOUNT OF TIME SPENT IN EACH ACTIVITY	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER OF HOURS	PER CENT
In bed, sleeping	33	10.2	57	15.7	90	13.1	8	33.3
In bed, awake	38	11.7	18	5.0	56	8.2	0	0.0
Mild-to-moderate	161	49.7	190	52.3	351	51.1	13	54.2
Strenuous	92	28.4	98	27.0	190	27.6	3	12.5
Unknown	126		37		163			
Total	450	100.0	400	100.0	850	100 0	24	100 0

activity. The category "in bed awake" should be discarded in this analysis, since many of the men may have gone to bed because they felt ill.

The analysis shows that the proportion of attacks occurring during strenuous activity was more than twice as great as the proportion of time spent in such activity, that the proportion of attacks occurring during mild or moderate activity was about equal to the proportion of time spent in such activity, but that the proportion of men stricken while asleep was but one-third of what would be expected on the basis of the time normally spent in sleeping. Numerically, the proportion of men engaged in strenuous activity, mild and moderate activity, and sleeping at the time of attack was as 222 to 93 to 39. In the group of fatal cases, more than 75 per cent of the men died rapidly of coronary insufficiency without infarction, whereas in the group of survivors, it may be assumed that most, if not all, had coronary artery occlusion with myocardial infarction; yet the percentages of types of activity for the two groups are strikingly similar.

When an analysis was made of the fatal cases to determine any possible correlation between the type of activity when the soldier was stricken and the type of lesion of the coronary arteries (simple narrowing, practically complete sclerotic occlusion, or thrombotic occlusion) with or without acute myocardial infarction, no correlation was found. However, when an analysis was made of those cases in which there was coronary artery thrombosis in relation to the type of activity when the soldier was stricken, evidence was found to allow the conclusion that there may be a correlation between the age of the obturating thrombus (fresh, organizing, or old) and the type of activity at the time of the attack. Only 11 per cent of those patients with coronary artery thrombosis who died in bed had old or organizing thrombi, whereas 27 per cent of those engaged in mild or moderate activity and 38 per cent of those engaged in strenuous activity had such thrombi (Table XV). Thus, by percentage there were

TABLE XV. AGE OF THROMBUS IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE IN RELATION TO ACTIVITY AT ONSET OF ACUTE ATTACK

AGE OF THROMBUS	ACTIVITY						TOTAL	
	IN BED		MILD OR MODERATE		STRENUOUS			
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Old or organizing	3	11.1	21	27.3	15	37.5	39	27.1
Fresh	24	88.9	56	72.7	25	62.5	105	72.9
Total	27	100.0	77	100.0	40	100.0	144	100.0

three times as many with old or organizing thrombi among those stricken while engaged in strenuous activity as among those found in bed when stricken. From these data it may be concluded that in some cases a thrombus or infarct may have been forming silently for some time and the type of activity at the onset of symptoms was purely coincidental; but that in other cases the type of activity,

particularly if strenuous, may have caused the additional demand for coronary blood flow that precipitated the fatal attack of coronary insufficiency. In the former cases the precipitating factor of the terminal event is unknown but may have been any of several, one of which may have been a generalized vascular relaxation in the presence of a very labile vasomotor system, rather than the much talked of constriction of the coronary arteries.

In the correlation of the presence of fresh thrombi at autopsy with the type of activity, it was found that 89 per cent of thrombi of patients who were in bed were fresh, as compared with 73 per cent of those in patients engaged in mild or moderate activity and 63 per cent of those in patients engaged in strenuous activity. It might be concluded from these figures that rest is more favorable for the formation of thrombi than activity and that death is more likely to occur when the patient with a fresh thrombus is at rest than when he is active; but it cannot be denied that activity may play a part in the production of thrombi. It would appear that although the state of the circulation during sleep is more favorable for thrombosis in a sclerotic artery, it is not as conducive to acute coronary insufficiency as activity when the thrombus is old.

In some cases in which death occurred suddenly, there were features of interest and probable importance in precipitating death. Seventeen men died during or soon after an alcoholic debauch. Seven men, all apparently good swimmers, died while swimming. Five men died during or a few days after a surgical procedure; one, during operation for purulent appendicitis; one, nine days after herniorrhaphy; one, seven days after extraction of teeth; one, two days after incision of a furuncle of the cheek; and one, suddenly after circumcision with local anesthesia. One man died twenty minutes after nicking his finger on a nail; two had had upper respiratory infections a few days before; two were apparently convalescing in hospital from pneumonia; one was convalescing in hospital from chickenpox; one had been treated for sore throat by means of sulfadiazine three days before; and one had had "dysentery" one week before death. One man had been ambulatory for three weeks after an attack of pneumonia when he died suddenly. One man had been struck in the chest by a volley ball two months before death. Another had been struck in the epigastrium with a rock one month before he died.

Analysis of the relationship between the ages of the men and their activity when stricken gave no indication that age was correlated with this factor within the age limits of this series. Neither was there a relationship between the height-weight factor and the type of activity preceding death.

PREVIOUS CARDIAC HISTORY

Of the 450 cases in which necropsy was performed, a previous history was recorded in 242 cases; in 183, death occurred so abruptly that a history was either not obtainable or not reliable, and in twenty-five, a history was either not obtained or not recorded. In these twenty-five cases, the probability is that in most there were no antecedent manifestations of cardiac disease. On the other hand, a careful history was obtainable in all of the 400 cases in which the soldiers sur-

vived. As a result, the history was known and was fairly reliable in 642 of the entire series of 850 cases.

The symptoms preceding the attack were divided into those which were definitely cardiac in origin and those which were of possible or even probable cardiac nature. Table XVI gives the figures relative to the previous cardiac history for the fatal cases and the survivors. In the two groups, the percentages of definite previous cardiac manifestations and of possible ones are almost identical, the percentages for the whole series being 51 with no previous cardiac history, 9 with "premonitory symptoms" which occurred within three weeks of the "attack," thirty-one with a definite history of previous cardiac symptoms for three weeks or more, and nine with a history of possible cardiac symptoms three weeks or more before the attack.

TABLE XVI. PREVIOUS CARDIAC HISTORY OF FATAL AND NON-FATAL CASES IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE

PREVIOUS CARDIAC HISTORY	FATAL CASES		SURVIVORS		TOTAL	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
None	123	50.8	202	50.5	325	50.6
"Premonitory" symptoms within three weeks	26	10.7	34	8.5	60	9.3
Definite symptoms (more than three weeks)	65	26.9 }49.2	137	34.2 }49.5	202	31.5 }49.4
Possible symptoms (more than three weeks)	28	11.6	27	6.8	55	8.6
Total	242*	100.0	400	100.0	642	100.0

*The total of 242 is obtained by subtracting 183, the number of men who died so abruptly that the history was either not obtainable or may have been incomplete, and 25, the number of cases in which the history was unknown.

Previous Cardiac Histories of the Fatal (Autopsied) Cases.—Definite or possible cardiac symptoms were said to have been present in 119 of the 242 fatal cases in which a history was obtained. In twenty-six (11 per cent), the symptoms preceded the attack by less than three weeks; therefore, they are arbitrarily designated as premonitory symptoms and as such are considered later in the paper. The symptoms in the other ninety-three cases occurred three weeks or more before the "attack." Of these, in sixty-five (27 per cent) the symptoms were definitely of cardiac origin and in twenty-eight (12 per cent), were possibly or even probably of such origin.

Of the sixty-five cases in which there were definite cardiac symptoms three weeks or more before the "attack," the symptoms were in the nature of anginoid attacks in fifty-seven patients and of partial or complete congestive failure in the other eight. In four patients the anginoid attacks occurred three weeks before death; in one, five weeks; in one, seven weeks; in one, "some weeks"; in six, one month; in three, between one and two months; in eight, between two and three months; in two, five months; in two, six months; in three, between five

and eight months; in one, eight months; in two, ten months; in one, "several months"; in seven, one year; in one, four years; in three, "several years"; in eight, an unstated time; in one, "as long as his friends could remember"; in one, as "repeated attacks"; and in one, "for quite some time."

The pain was substernal in fourteen soldiers; precordial in three; "anginal" in five; precordial, radiating to the left arm in three; precordial, radiating to the arms in one; substernal, radiating to the elbows in one; in the "upper chest," radiating to the shoulders and arms in two; epigastric and substernal with "gas" in one; epigastric and precordial, with palpitation, sweating, and choking in one; precordial with wheezing and dyspnea in one; in the left shoulder and arm followed by precordial pain in one; "in the chest" in one; under the left scapula in one; in the left axilla in one; in the precordium and back in one; and in the left elbow in one. The pain was epigastric with a tight feeling in the arms in one patient. It appeared as tightness in the "chest" and radiated down the arms in one; as discomfort, or vague or evanescent pains, or pains not described in seven; and as "similar to the final pain" in three. Nine men had had anginal pain associated with dyspnea, one with palpitation, choking, and sweating, and one with burning in the throat.

Descriptions of some of the attacks were of interest. One man who had had four attacks of epigastric and precordial pain associated with palpitation, sweating, and choking in the preceding year had been hospitalized twice and on both occasions had returned to full duty. Another man had been hospitalized for two and one-half months because of precordial pain, wheezing, and dyspnea. Another had been hospitalized two weeks before the terminal illness because of chills, chest pain, and cough. Another had had one attack of anginal pain one year before which was diagnosed coronary thrombosis. One man who had had anginal attacks for seven months before death had been hospitalized for one month, six months before with the diagnosis of coronary thrombosis. Another had been hospitalized because of precordial pain with dyspnea one year before and discharged as well; eight months before death he had had a typical attack of myocardial infarction followed by persistent congestive failure. He was found to have an old anterior infarction resulting from thrombotic occlusion of the anterior descending artery. Another man had had pain across the upper chest and arms with nausea, vomiting, diarrhea, and sweating seven weeks before, followed by abdominal pain. This attack was considered a gastrointestinal upset, but although the man had been digitalized because of tachycardia, he had been allowed to be out of bed off and on until he died. One soldier had had an attack of substernal pain radiating to the elbows, lasting five hours, while flying one month before death, followed by another attack the next day, again while he was flying; but there were no more attacks until the night before he died.

As to the frequency of anginoid attacks, six men had had one attack, two had had two attacks, two had had three attacks, three had had four attacks, one had had five attacks, thirteen had had repeated attacks of unstated frequency, and the number was not given for the others.

In a few cases the factors inducing attacks were given; these included exertion, eating, deep breathing, and rest. Some attacks were relieved by rest, belching, vomiting, or deep breathing.

The duration of attacks was rarely given. Three men had had anginal symptoms for four days, one for five days, one for several days, and one for one week. In one patient in whom there had been three bouts of substernal pain at rest and after eating seven weeks before and two bouts after exertion just before hospitalization, the attacks lasted as long as two hours. In another patient in whom there had been one attack of precordial pain one year before the terminal illness, the duration was thirty minutes.

Nine men with anginoid attacks had been hospitalized within seven months of death because of symptoms undoubtedly caused by cardiac disease, although that diagnosis was not made. One had been in the hospital for three weeks one month before death because of attacks of tachycardia followed by dizziness, precordial pain, pain in the left arm and hand, dyspnea, and weakness. The discharge diagnosis was neurocirculatory asthenia. Another had been hospitalized for two weeks two months before death because of tiring on walking; he had epigastric pain, dyspnea on exertion, and excessive perspiration; tachycardia without exertion had been present for two years. He was discharged to duty seven weeks before death, which occurred suddenly while he was drilling. This man was 26 years old, which may account for the medical officer's failure to suspect cardiac disease and request electrocardiographic examination. A third man had been hospitalized two months before death for three weeks because of anginal attacks. An electrocardiogram showed questionable changes, and the diagnosis of neurocirculatory asthenia was made. Another man had been examined at a station hospital three weeks before death because he complained of a dull, heavy, aching pain in the left anterior thoracic region, which had been present since he had been struck there by a medicine ball two months before. Two weeks prior to examination he had also had an attack of epigastric pain and vomiting. Another man was hospitalized for eleven days two months before death because of pain in the chest and dyspnea, both on exertion, of three weeks' duration. The electrocardiogram showed the T wave in Lead IVF to be inverted. On the date of death he reported to the Emergency Room, stating that he had continued to have pain in the chest radiating to the right shoulder after exertion. While leads were being connected for an electrocardiogram he began to gasp for breath and died within a few minutes. Three other cases were similar to this; the patients had been hospitalized for three months, one month, and three weeks, respectively, before death, but a definite diagnosis was not made. The ninth patient had been hospitalized seven months before death for a period of two weeks. Four nights before admission he had awakened with a substernal burning sensation lasting from five to ten minutes; the pain recurred on exertion but was relieved by rest. Examination revealed a small diverticulum of the stomach and a questionable ulcer crater in the duodenum. Electrocardiograms were made on three days. They showed slurred QRS complexes, inverted T wave in Lead IV F, late inversion of T in Lead CF_3, and very slight late inversion of T in Lead CF_5.

Eight of the sixty-five men with definite cardiac symptoms three weeks or more before the "attack" had had symptoms of total congestive failure or of left ventricular weakness. Of the fifty-four men in the autopsy series who were hospitalized during their final illnesses, five had had congestive failure prior to hospitalization. In one man it had been recurrent for seven months before death, and in the others it had existed eight months, four months, three months, and one month, respectively, before the terminal illness. The man who had had congestive failure for eight months had had acute myocardial infarction at the onset of the congestive failure, and the soldier who had had failure for four months had been hospitalized for eight months prior to the onset of failure with a diagnosis of coronary thrombosis. Dyspnea on exertion, other than in the cases of congestive failure already noted, was complained of in three cases; in one patient this symptom had been present one year before and had been associated with a burning sensation in the throat; in one patient it had been present for five months; and in one patient, who had also had nocturnal attacks, it had existed for three weeks.

There were twenty-eight men (12 per cent) who had had symptoms three weeks or more before the "attack" which, in retrospect, were probably of cardiac origin. Ten men had had abdominal pain: one as a dull, aching, epigastric pain one hour after meals for three years; one as attacks of epigastric pain with dyspnea and tachycardia for two years; one with attacks of vomiting for one year; one as vague abdominal pains for "a long time"; one as attacks of epigastric pain, vomiting, and flatulence for seven months; one as left-sided abdominal pain on exertion for five weeks; one as epigastric pain related to meals for one month; and one with "indigestion" after eating. Another man had had epigastric or abdominal pain of such severity two and one-half months before that cholecystectomy had been performed. One man had been told he had an ulcerated stomach one year before.

Three other men had had "indigestion." Another soldier had had diarrhea, vomiting, and fever three months before death and mild abdominal pain with diarrhea for three days before death.

One man had had fainting attacks two years before death; another, spells of weakness and fatigue for one month; another, a spell of weakness one month before death; another, an attack of syncope two months before the terminal illness; and another, "falling out" spells. One man had had attacks of nervousness and sweating for an unstated period, and another, recurrent spells of nervousness and psychic depression during the year before death. One man had had three convulsive seizures in the preceding eleven months. Another had had "asthma" for three weeks eleven years before death.

Two men had had palpitation and tachycardia, one for six months, the other for one month. Another man had had occasional attacks of tachycardia for an indefinite period; he was hospitalized two weeks before the terminal illness with chills, chest pain, and cough.

One man had had slight dyspnea and a tired feeling on exertion for an unstated period. Another had had "cramping pains" in the legs and arms

unrelated to effort for one month; another, pain in the muscles of the legs for two months.

Other facts of interest in the histories of the fatal cases are as follows:

One man had been treated for heart trouble for a year, and another had been hospitalized for nine months for heart trouble and discharged two months before death. One man had been hospitalized for ten days with the diagnosis of chronic nephritis which was not confirmed at autopsy.

In four cases the diagnosis of neurocirculatory asthenia had been made one to two months before death.

Six men had been in a hospital for complaints other than cardiac at the time of death. One of these men had been feeling nervous, irritable, and under tension for three months; four hours before death he became disorientated and was removed to the hospital in a state of alternating dyspnea and convulsions in which he died. Two men* were apparently recovering from pneumonia; one* was convalescing from chickenpox; one* was being operated on for purulent appendicitis; one* had had a herniorrhaphy nine days before death; and one was in the hospital for twenty-four hours with the tentative diagnosis of peptic ulcer.

Only five men were believed to have had previous hypertension, one paroxysmally. In one patient the heart weighed 575 grams, in three it was of normal weight, and in one the weight was not given, the heart presumably being of normal size.

Previous Cardiac Histories of the Men Who Survived.—A definite statement in reference to a past history of cardiovascular disease was available in all 400 cases. Two hundred thirty-six men gave no history of cardiovascular disease before the acute attack. Seventy-three gave a definite history of rather typical angina of effort, sixty-four presented a history of "coronary insufficiency" or other symptoms indicative of pre-existing heart disease, and twenty-seven presented symptoms that indicated possible heart disease, all three weeks or more before the "attack." In addition, there were thirty-four men who had "premonitory" symptoms within three weeks of the "attack." Nineteen men had a knowledge of high blood pressure before the onset of the "acute attack," and six stated that they had had rheumatic fever in childhood but had no symptoms or history suggesting cardiac involvement.

Among the seventy-three soldiers with a typical syndrome of angina of effort, there was a wide range in the length of time that the symptoms were present before the actual "acute coronary attack." One man had had anginal attacks for three weeks, one for four weeks, three for six weeks, three for eight weeks, three for ten weeks, one for four months, three for five months, twelve for six months, six for eight months, two for nine months, fourteen for one year, two for one and one-half years, three for twenty months, three for two years, one for two and one-half years, one for three years, one for five years, eight for "many" years, and four for an unspecified time.

Of the sixty-four patients with a history indicating "coronary insufficiency" preceding the "acute coronary attack" that resulted in discharge from the Army,

*Previously noted.

eleven not only described typical symptoms of a previous "coronary attack" before they entered the Army, but such a diagnosis had been made by their civilian physicians. Four of them had had attacks one to one and one-half years before; five, about two years before; one, three years before; and one, four years before. All of these men had been hospitalized for from four to eight weeks and had been told they had a "heart attack," but none revealed his history at the time of induction.

Thirteen of the fifty-three remaining patients with a history of symptoms indicative of heart disease had experienced an attack similar to but not as severe as the acute episode in the Army. One patient had had two attacks similar to the present "acute attack" ten years earlier at the age of 23 years; these attacks were less severe than the recent one and the patient had not consulted a physician. One soldier had a similar attack three years before; the pain lasted two hours and the patient was kept in bed for two days, but the physician did not determine the cause of the symptoms. Another man had been kept in bed for one week after a similar attack of severe chest pain three years before, when the diagnosis of neurocirculatory asthenia was made. One man reported an attack like the present one five years earlier, but no physician had been consulted. In another patient a similar attack two years before the "coronary attack" in the Army was diagnosed as neuritis of the left chest. Another veteran had experienced excruciating pain in the chest while playing tennis two years earlier. His physician had told him that he had overtaxed his heart and had kept him in bed for five days; ever since this episode the man had been short of breath on exertion. One man had had a similar attack two and one-half years earlier in which the pain in the chest was followed by loss of consciousness for one-half hour; the attending physician had not given the patient a definite diagnosis. One patient reported a similar attack one year before, but he had not consulted a physician. Two men had experienced similar attacks six months before the "acute coronary attack": In one case, the substernal pain lasted one hour, and in the other, the pain was of very short duration, but since then the patient had been short of breath on slight-to-moderate exertion. Neither man had consulted a physician. One soldier had had a severe chest pain nine months before the main attack; the pain, however, lasted only a few minutes and was followed by symptoms attributed to "indigestion." One patient had had substernal pain four months earlier while in the Army but had not reported the incident to the medical officers. One month before the acute episode, another soldier had experienced chest pain similar in náture but of shorter duration than that of the "acute coronary attack"; he also had not reported.

In seventeen other cases of the fifty-three in which the previous history was indicative of cardiac disease, pain was the outstanding symptom. This pain was somewhat different from that described in the preceding paragraph in that it was not similar to the pain of the "acute coronary attack" that occurred in the Army. One patient had had chest pains for twenty years, beginning when he was about 15 years of age, accompanied by shortness of breath; these symptoms were present irregularly but were not definitely associated with exertion. Another soldier had had severe upper abdominal pain ten years before while being

treated for gastric ulcer; at that time his physician told him that the pain was probably due to heart disease. One man had experienced an attack of chest pain diagnosed as being of cardiac origin but not considered indicative of organic heart disease. Three years before the "acute coronary attack," one patient was hospitalized for pain in the upper abdomen; an electrocardiogram had been taken but no definite diagnosis established; the pain had recurred at least every four weeks but was not associated with exertion. One soldier had had precordial pains for two years, with four or five attacks a month, lasting one minute and not related to exertion. Another man had had an attack two years before the acute attack; the pain occurred twice during training and was located in the left axilla. Three men had had attacks of chest pain one year before the "coronary attack." One of these men was referred to a cardiologist for study because of epigastric pains, but the diagnosis of cardiac disease was not made. Another had had a sudden chest pain of short duration; the pain radiated down both arms and was followed by a brief period of unconsciousness. After being kept at rest for five days, the soldier was returned to active Army duty. The third man had experienced a sudden, severe retrosternal pain while moving heavy boxes; the pain lasted three hours and then disappeared without medical treatment. Seven men had had definite attacks of substernal or precordial pain from two to six months before the "real coronary attack." One man had had dull, aching, precordial pain for six months, usually while he was at rest and never associated with exertion. Another soldier was awakened from sleep five months before the "attack" by a sudden severe pain over the left chest; the pain lasted thirty-six hours, and the soldier did not seek medical attention or remain inactive. Three men had had pain three months before the "acute attack." One had had a sudden attack of precordial pain that lasted one hour; another had noted a severe chest pain that lasted only a few minutes but caused him to sit down to rest; and the third man experienced pain between the scapulae of very short duration and not associated with exertion.

Twenty-three of the fifty-three patients experienced symptoms other than pain and their histories were suggestive of cardiac disease before the "acute coronary attack." In twelve of these cases shortness of breath on exertion was the main symptom. One soldier recalled that dyspnea had been present for "years"; another dated the onset of this symptom back ten years. Six men had had shortness of breath on exertion for from one to four years preceding the coronary attack; one had had dyspnea for five months before the attack; and another had had symptoms for three months. Eight of these men had other symptoms referable to the heart before the "acute attack." One had had a severe attack of palpitation ten years earlier; another recalled a few days of "irregular beating" four years before. One man gave a history of severe smothering spells one year before; since then he had had to drop out of drill because of frequent recurrences. Two men had noted a tightness over the chest associated with difficulty in breathing; these symptoms disappeared after a short rest and did not recur. One man had had a choking sensation in his throat one month before the "attack." One soldier had been told three years previously that

because of his heart his life insurance premium would be higher. Another soldier had stated at induction that he thought that he had heart trouble.

There were three other patients who gave a definite past history of heart disease. Two of these men had been told by their private physicians that they had cardiac enlargement; one had experienced an episode of heart failure two years before but did not know the cause.

Nineteen men stated that they had definite knowledge of high blood pressure before the "acute coronary attack." These elevated blood pressures had been discovered on routine physical examinations for various purposes and, in almost all instances, were not responsible for any symptoms as far as the patient knew.

There were twenty-seven cases in which the history of symptoms previous to the "acute coronary attack" was suggestive of possible cardiac disease. In seventeen, dyspnea on exertion was the outstanding symptom. Two men had had dyspnea for two months before the acute "attack," two for six months, three for one year, five for two years, one for three years, one for four years, one for twenty years, and in two cases the duration was not recorded.

In five cases, upper abdominal distress or pain was the outstanding symptom. One soldier had experienced pain in the epigastrium for six years and had been told that it was due to a stomach condition. One man had had epigastric distress after meals for three years; another for five years had had vague abdominal pains, relieved by soda, and dyspnea which made it necessary for him to sleep with several pillows because of shortness of breath. One veteran reported severe attacks of nausea and epigastric pain attributed to gastritis; there was no similarity between these symptoms and those during the "acute coronary attack." One man over a period of months had had frequent epigastric burning, relieved by soda.

Two men had had intermittent pain over the left chest; it was fleeting, did not radiate, and usually occurred at rest. This symptom had been present for two years and five years, respectively. One man had experienced a severe aching pain in the anterior thighs for one week, five weeks before the acute attack. One soldier had had severe "smothering spells" on three occasions during the year preceding the acute attack. One man had noted fainting and dizzy spells on bending or stooping for several years before the "acute coronary attack."

Premonitory, Preliminary, or Prodromal Manifestations.—The subject of premonitory manifestations of acute coronary artery occlusion is a difficult one to discuss, since any anginoid form of attack, except in established cases of angina pectoris, should be considered to be premonitory until proved otherwise. Of the 242 fatal cases in which a history could be obtained, there were twenty-six in which prodromal manifestations occurred within three weeks of the final phase of the "attack"; there were thirty-four similar cases among the 400 survivors. The symptoms, however, were not significantly different in many cases from symptoms that occurred months and even years before the last episode. Among the fatal cases the symptoms occurred within twenty-four hours in seven cases, within thirty-six hours in one case, within two days in three cases,

within three days in one case, within four days in four cases, within six days in one case, within one week in one case, within eleven days in one case, within several days in one case, within two weeks in three cases, and within three weeks in two cases. Among the survivors the symptoms occurred within two days in one case, within three days in one case, within four days in two cases, within five days in three cases, within one week in four cases, within eight days in one case, within nine days in two cases, within ten days in three cases, within eleven days in one case, within two weeks in six cases, within sixteen days in one case, and within three weeks in nine cases.

Examples of these cases are as follows: One man had pain and a sense of constriction in the upper sternal region one day and again four days later, at which time an electrocardiogram was normal; nine days later he had another attack lasting two hours, when he died. Another had diarrhea on one day and a week later had pain in his right shoulder lasting ten minutes; later the same day he had substernal pain and died. Another man had epigastric pain with "indigestion" and tightness in the chest radiating down both arms, relieved by the use of alkalis; four days later he developed pain in his chest and died. Another man had an ache in his chest and epigastrium, shooting to his back intermittently for several days; on the day of his death he had severe epigastric pains, became unconscious for ten minutes, then sat up in bed and fell over dead. Two days before death a soldier developed severe dyspnea on exertion; he was found dead in bed. Another had both nocturnal dyspnea and dyspnea on exertion for three weeks; he was in the hospital for forty-three days thereafter with signs of pulmonary congestion and died without having had pain at any time. One week before his "coronary attack" a veteran had an attack of nausea with severe burning pain extending from the epigastrium to the neck with weakness of the left arm; twenty-four hours before his severe attack of substernal pain he had a similar attack. Another man had a severe constricting type of pain across the anterior part of the chest accompanied by dyspnea, the attack lasting between one and two hours and being relieved by rest; he was hospitalized for one week, all findings being normal, and returned to duty; his "coronary attack" occurred on the sixteenth day following the first attack of pain. Three weeks before his "coronary attack" a soldier had excruciating pain in the anterior part of the chest; hospitalization was advised, but the man refused and the pain ceased after four hours; the next day the pain recurred with slight exertion but did not reappear until twenty days later when he was going through an obstacle course. Another man had precordial pain and epigastric discomfort with radiation to the left shoulder and arm lasting several hours; he remained on duty but was easily fatigued, and ten days later he had his "coronary attack." Another man had a tight feeling in his chest with dyspnea and nausea lasting six hours; his symptoms recurred the next day while he was running, but he was free of symptoms for four days, when he had a typical "attack." Another man, while walking leisurely, suddenly experienced substernal pain with a sense of heaviness and aching in the shoulder and elbows, the symptoms ceasing with rest after ten minutes; twenty such attacks occurred within nine days, when his major attack developed. Another soldier had had typical angina of effort for a year, but fourteen days

before his severe attack he had a severe pain with dyspnea and a choking sensation while at rest, these symptoms lasting two hours; this syndrome was repeated four days later, but he was symptom free until the "real attack" occurred. While working in a kitchen, a soldier had moderate pain across the lower anterior chest region which lasted a few hours and disappeared only to recur each day for three days; he was free of symptoms for four days, when his severe attack occurred while he was resting. Another man was awakened from sleep with a severe, pressing substernal pain which lasted for one hour, after which he went back to sleep; seven days later he had a similar pain with dyspnea, and six days after that, a recurrence while he was playing cards; he was symptom free for a week, when his "coronary attack" occurred. A baker, while kneading dough, felt pain in the left side of his chest which radiated down his left arm and lasted ten minutes; he felt well thereafter and continued to work until he had a classical attack one week later. The other cases were, in general, similar to these.

Correlation of Previous Cardiac History With Various Lesions Found at Necropsy.—There was no significant evidence that the presence or absence of a previous cardiac history in the fatal cases was correlated with the presence or absence of simple narrowing as the sole lesion of the coronary arteries, or with the presence or absence of sclerotic occlusion of the coronary arteries, or with the presence or absence of thrombotic occlusion of the coronary arteries.

Patients with a definite history of cardiac symptoms tended to have myocardial infarcts more frequently than did those without it; the frequency being 39 per cent in the former group as compared with 22 per cent in the latter (Table XVII). Similarly, there was a greater tendency for such patients to have myocardial scars, the percentages being 77 and 62, respectively (Table XVIII), indicating that scars mean more frequent or more severe previous coronary insufficiency.

TABLE XVII. PREVIOUS CARDIAC HISTORY IN RELATION TO MYOCARDIAL INFARCTS AMONG MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE

MYOCARDIAL INFARCTS	PREVIOUS CARDIAC HISTORY					
	NONE		DEFINITE		POSSIBLE	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
None	97	77.6	40	61.5	22	78.6
Gross	22	17.6	23	35.4	4	14.3
Microscopic	6	4.8	2	3.1	2	7.1
Total	125	100.0	65	100.0	28	100.0

A history of previous definite or possible cardiac disease was given in approximately one-sixth of the cases with simple narrowing alone, in one-fourth of the cases with sclerotic occlusion, in one-fourth of the cases with thrombotic

occlusion, in one-fourth of the cases with gross myocardial infarction, and in somewhat less than one-third of those with myocardial scars.

There was no indication that the presence or absence of a previous cardiac history was related to the age of coronary artery thrombosis (recent, organizing, or old) when it was present.

TABLE XVIII. PREVIOUS CARDIAC HISTORY IN RELATION TO MYOCARDIAL SCARRING AMONG MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE

SCARRING	PREVIOUS CARDIAC HISTORY					
	NONE		DEFINITE		POSSIBLE	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
None	48	38.4	16	24.6	13	46.4
Diffuse	46	36.8	30	46.1	12	42.9
Focal	26	20.8	15	23.1	2	7.1
Both	5	4.0	4	6.2	1	3.6
Total	125	100.0	65	100.0	28	100.0

Duration of Terminal Illness of the Fatal Cases and Correlation With Various Lesions.—Of the 450 fatal cases, death occurred within twenty-four hours of the onset of symptoms in 375 (83 per cent), the exact duration being known in 328 and unknown in forty-seven (because the men were found dead or dying). This suddenness of death in such a large percentage indicated the inability of the coronary circulation of these men to compensate for acute obstruction or for other factors that induce acute coronary insufficiency. Table XIX shows the duration of the terminal illness of the 450 cases.

TABLE XIX. DURATION OF TERMINAL ILLNESS IN FATAL CASES OF CORONARY DISEASE AMONG MEN 18 TO 39 YEARS OF AGE, INCLUSIVE

DURATION	NUMBER		PER CENT	
Less than twenty-four hours	375		83.3	
Instant death, seconds		138		30.7
1-5 minutes, few minutes		67		14.9
6-15 minutes		18		4.0
16 minutes to 1 hour		15		3.3
1-2 hours		30		6.7
3-11 hours		26		5.8
12-23 hours		9		2.0
Several hours		25		5.5
Unknown		47		10.4
Twenty-four hours or more	75		16.7	
1-6 days		33		7.4
1-2 weeks		21		4.7
½-1 month		5		1.1
1-3 months		14		3.1
4-7 months		2		0.4
Total	450		100.0	

A comparison was made between the cases in which the terminal illness was less than twenty-four hours and those in which it was twenty-four hours or more. Overall, there was no significant tendency for age to be related to the duration of the terminal illness. However, a somewhat larger proportion of the men whose terminal illness lasted twenty-four hours or more were 35 to 39 years of age than those whose terminal illness lasted less than twenty-four hours.

It was found that of the men whose previous histories were known, 61 per cent who had died within twenty-four hours had definite or possible previous manifestations of cardiac disease, as compared with 52 per cent of the men who lived twenty-four hours or more.

A comparative analysis of the lesions gave no significant indication that the duration was correlated with the presence or absence of simple narrowing as the sole lesion of the coronary arteries, since about 80 per cent of the men of both groups died within twenty-four hours; or with the presence or absence of sclerotic or thrombotic occlusion of the coronary arteries.

As was to be expected, more men with thrombotic occlusion and with myocardial infarction lived "longer," that is, had a significantly longer terminal illness, than those having thrombotic occlusion but no infarction.

In only 2 per cent of the patients who died suddenly (within twenty-four hours) and who had a previous cardiac history were there gross myocardial infarcts, as compared with 27 per cent of the patients in whom the terminal illness lasted twenty-four hours or longer and in whom there was also a previous cardiac history.

Gross myocardial infarcts were observed in 13 per cent of the patients who died suddenly and had no previous history, as compared with 36 per cent of the patients in whom the terminal illness was twenty-four hours or more but in whom there was also no previous cardiac history.

The presence or absence of myocardial scars was not correlated with the duration of the terminal illness, but the patients with scarred hearts and a previous cardiac history tended to live longer. Likewise, there was no indication that the age of coronary artery thrombosis (recent, organizing, or old) was correlated with the duration of the terminal illness, whether there was a previous cardiac history or not.

As might be expected, there was a highly significant indication that the presence of a mural thrombus was related to a duration of the terminal illness of twenty-four hours or more, since infarction is the main cause of mural thrombus formation in this series.

(To be continued)

THE STRESS AND THE ELECTROCARDIOGRAM IN THE INDUCED HYPOXEMIA TEST FOR CORONARY INSUFFICIENCY

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THE induced hypoxemia test has been established as a procedure which plays a small but useful role in the diagnosis of coronary sclerosis.[1-3] Proper emphasis has been placed upon the potential dangers of the test.[4] However, if the patients to be subjected to the procedure are properly selected and if precautions in administration of the test are observed, the danger entailed is minimal and does not contraindicate use of the test as a diagnostic adjunct. In the 730 tests carried out at the Mayo Clinic for the diagnosis of coronary sclerosis, no fatalities have occurred. It is now believed that in the majority of the patients who have had an alarming reaction, the patient's age or his affliction by complicating illnesses were etiological factors. The factor of danger, however, does limit application of the procedure in many investigations of clinical and electrocardiographic problems of coronary insufficiency, in which otherwise it would be most valuable.

Other undesirable results that might mitigate the usefulness of the test, even as a diagnostic adjunct, have been considered to be (1) its contribution to errors in diagnosis which occur when a negative reaction to the test is used as a basis for the exclusion of coronary disease, or when a reaction is called positive on the basis of minimal electrocardiographic change, or when a positive reaction obscures the diagnosis in the patient whose symptoms are secondary to a disease other than coronary sclerosis, and (2) unnecessary increase in the cost of and time consumed by a cardiac examination. These undesirable consequences, we believe, can be avoided by a proper conception of the purpose of the test and a sound interpretation of the results obtained.

While our efforts have been directed mainly toward an evaluation of the usefulness of the hypoxemia test as a diagnostic adjunct, the following problems which are related to the application and interpretation of the test have frequently recurred in our minds: The possibility of localizing the segmental coronary sclerosis; the influence of ventricular hypertrophy on the electrocardiographic changes which result from hypoxemia; the application of results of the test to prognosis and to the evaluation of drug therapy and of surgical risk; and, finally, the reasons for the frequent dissociation of the electrocardiographic and pain responses. While many of these problems remain unanswered, in others we shall present some theoretical and experimental explanations.

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Among the tests carried out at the clinic, the number performed on patients with thoracic pain which was believed to be an atypical manifestation of coronary insufficiency is slightly greater than the number carried out on patients with puzzling thoracic distress which was believed to be noncardiac in origin. It is of interest that over a period of seven years, the number of tests performed each year has been about the same. About 10 per cent of the subjects have been physicians. The induced hypoxemia is carried out on about 2 per cent of all patients at the clinic on whom a diagnosis of coronary sclerosis is made.

TECHNIQUE

The actual technique of the test is similar to that of our earlier description.[2] The patient lies in a semireclining position and breathes from a tightly fitted mask a mixture of 10 per cent oxygen in nitrogen. There are unidirectional valves in the mask so that no rebreathing occurs. The mask is connected through a long, wide-caliber tube to a demand regulator which furnishes an adequate flow of the gas mixture no matter what the depth of the inspiration. A by-pass valve on the regulator may be opened, if desired, to give a constant flow. In the tubing between the regulator and the mask there is a T tube with an attached 4 liter rubber reservoir bag into which leads a small tube from the tank which contains 100 per cent oxygen. The regulator is equipped with a slight positive pressure arrangement to minimize the slight subatmospheric pressure in the mask during inspiration. The demand valve apparatus has three advantages over the old constant flow arrangement: (1) the mixture of gas is used economically, (2) the noise of the valve gives an additional check on the patient's respiration, and (3) ventilation rates can be measured. The mask should be fitted with care. When this was done, analyses of the gas within the mask revealed no significant leaks except in a few instances. Analyses of the tanks of oxygen-nitrogen mixture that have been supplied to us have disclosed an oxygen content averaging 10.3 per cent. The greatest variations from this figure have been 9.6 and 11.0 per cent. In this past year, the use of a direct writing electrocardiograph in the test has been of great value, in that the test may be terminated if and when diagnostic electrocardiographic changes appear.

INTERPRETATIONS

The criteria outlined by Levy[1] remain the basis for our interpretations. The exact summated measurements of S-T segment deviation are regarded as of lesser significance than the presence or absence of a type of change which, experience has taught, characterizes the hypoxemia response. The precordial lead in the apical area is by far the most diagnostic lead. Two types of change in this lead occur: the common one is the depression of the S-T segment of more than 2.0 mm. and the rarer change is reversal of the T wave. To be clearly significant, it is believed that the latter change should pertain to T waves of at least 0.3 millivolt.

In our previous article, the difficulty of the interpretation of a pain response was emphasized. Once again it may be said that a test in which the result depends upon an interpretation of the subjective responses of the patient fails to afford

evidence of a particularly useful kind. However, if the transition from a gas mixture which contains 10 per cent oxygen to one which contains 100 per cent oxygen is carried out unknown to the patient with pain, the immediate relief of distress usually may be relied upon as an indication of a positive reaction to the test.

EVALUATION OF THE STRESS

The fact that the results of the test are positive in only about 50 per cent of persons on whom the clinical diagnosis of coronary sclerosis has been made need not be surprising, but it stimulates one's curiosity concerning the factors essential to a positive result. In a subsequent part of this discussion, consideration will be given to the alterations in the responses of the myocardial cells to the excitatory process during the period of hypoxia. If these changes develop and if they produce in the electric field of the heart potential alterations which are manifest in the recorded electrocardiograms, then the reaction to the hypoxemia test is positive. A negative result of the test may be related either to failure of significant alterations in the electric field of the heart to be recorded or to failure of such alterations to develop. That appreciable changes in the electric field are commonly unrecognized, because of their failure to manifest themselves in the electrocardiograms which are recorded routinely, seems unlikely. Therefore, the explanation for the majority of the negative reactions to the test must be related to an actual absence of significant alterations in the sequence of potential changes related to the heart beat.

For the absence, during hypoxia, of appreciable alterations in the electric field of the heart affected by coronary sclerosis two explanations may be proposed. These are (1) that an area of injury does develop but is so distributed within the myocardium that for each dipole oriented in one sense there is another oriented in the opposite sense (in such a circumstance the resulting electric forces would cancel each other) and (2) that no area of injury develops. The latter is the simplest and probably the correct explanation for most of the negative reactions to the test. But acceptance of the latter explanation provokes an inquiry into those factors in cardiovascular function which determine whether or not such an area of injury develops in a heart affected by coronary sclerosis. Barach and co-workers[5] elucidated the problem, in part, by demonstrating the great difference in the arterial hemoglobin saturations among patients breathing mixtures low in oxygen and the protective effects of administering carbon dioxide. Further evaluation of the physiologic disturbances in normal persons breathing low concentrations of oxygen have been published very recently by Dripps and Comroe.[6] Their data supply further evidence of the variation in individual response in arterial oxygen saturation, ventilation, and cardiac output under hypoxemic conditions.

There are many factors, some rather intangible, that might contribute to the presence or absence of an area of injury within the myocardium. Among the many variables one has to consider are (1) the degree of increase in cardiac work during the test; (2) the degree of increase in oxygen demand for the same work due to dilatation of the heart (or epinephrine effect); (3) a difference in the amount of oxygen delivered to the myocardium from a unit of blood, which is

dependent upon the degree of desaturation of the arterial hemoglobin, the latter, in turn, being related to an increase or decrease in the pH of the blood as well as to unknown factors that limit the degree of desaturation of capillary blood; (4) the capacity of the blood vessels to permit a compensatory increase in coronary flow, a factor which is related, in turn, to the degree of stenosis and to the length of the stenosed part of the vessel; (5) possible variations in the redistribution of coronary flow and drainage; and (6) the amount of coronary vasoconstriction, which may be a response to acapnia, a part of a general reaction to pain, or a paradoxical reaction of diseased blood vessels. To certain of these factors more extended consideration will now be given.

(1) In order to determine cardiac work one needs values for both cardiac output and blood pressure; without measurements of cardiac output there are no available figures for the expenditure of energy by the heart. In certain patients in whom the test is performed, neither the blood pressure nor the pulse rate increases, although in most patients there is a rise in blood pressure of about 10 mm. of mercury, both systolic and diastolic, and an increase of 20 to 30 beats per minute in pulse rate. In a few patients there may be a more definite pressor response with increases in systolic pressure of 30 to 50 mm. of mercury and increases in diastolic pressure of 15 to 20 mm. of mercury, such reactions being usually associated with moderate tachycardia. A decrease in pulse rate of 10 to 30 beats without change in blood pressure is occasionally observed. Among the few unfavorable reactions, circulatory collapse with rapid fall in blood pressure is the most common. In our cases this condition was complicated on two occasions by cardiac asystole for as long as four seconds.

Except for one instance in which the electrocardiographic abnormality occurred during a marked hypotensive reaction, we have not observed any correlation between the results of the test and the behavior of the blood pressure and pulse rate. One must assume that the combination of hypertension and hypoxemia would increase the stress. Yet it has been particularly noted that those few patients on whom a probable diagnosis of coronary sclerosis was made on clinical grounds and who had a strong pressor response, gave also negative reactions to the test. Furthermore, in a certain number of patients with moderately severe, and in a few with severe hypertension, significant electrocardiographic changes did not develop during the test.

On the basis of the facts available, it appears justifiable to conclude that variations in cardiac work are a factor of minor significance in determining the outcome of the hypoxemia test.

(2) The possibility of an increased oxygen demand for the same work is largely theoretical at present and will not be discussed further at this time.

(3) Some data have been obtained bearing on the significance, in the production of electrocardiographic changes, of variations in the amount of oxygen delivered to the myocardium from each unit of blood. In the consideration of this factor it should be remembered that the cardiac venous blood is normally markedly desaturated, unpublished results obtained in our cardiovascular laboratory from catheterization of the coronary sinus in man having shown saturation values as low as 10 per cent.

As part of our routine test, we have determined the values for arterial hemoglobin saturation by means of an oximeter of the Millikan[7] type; marked variation in these values among persons who underwent the test has been observed (Fig. 1). The saturation drops rapidly, usually to values between 80 and 85, followed by a further gradual decrease. Frequently there may be a plateau appearance from

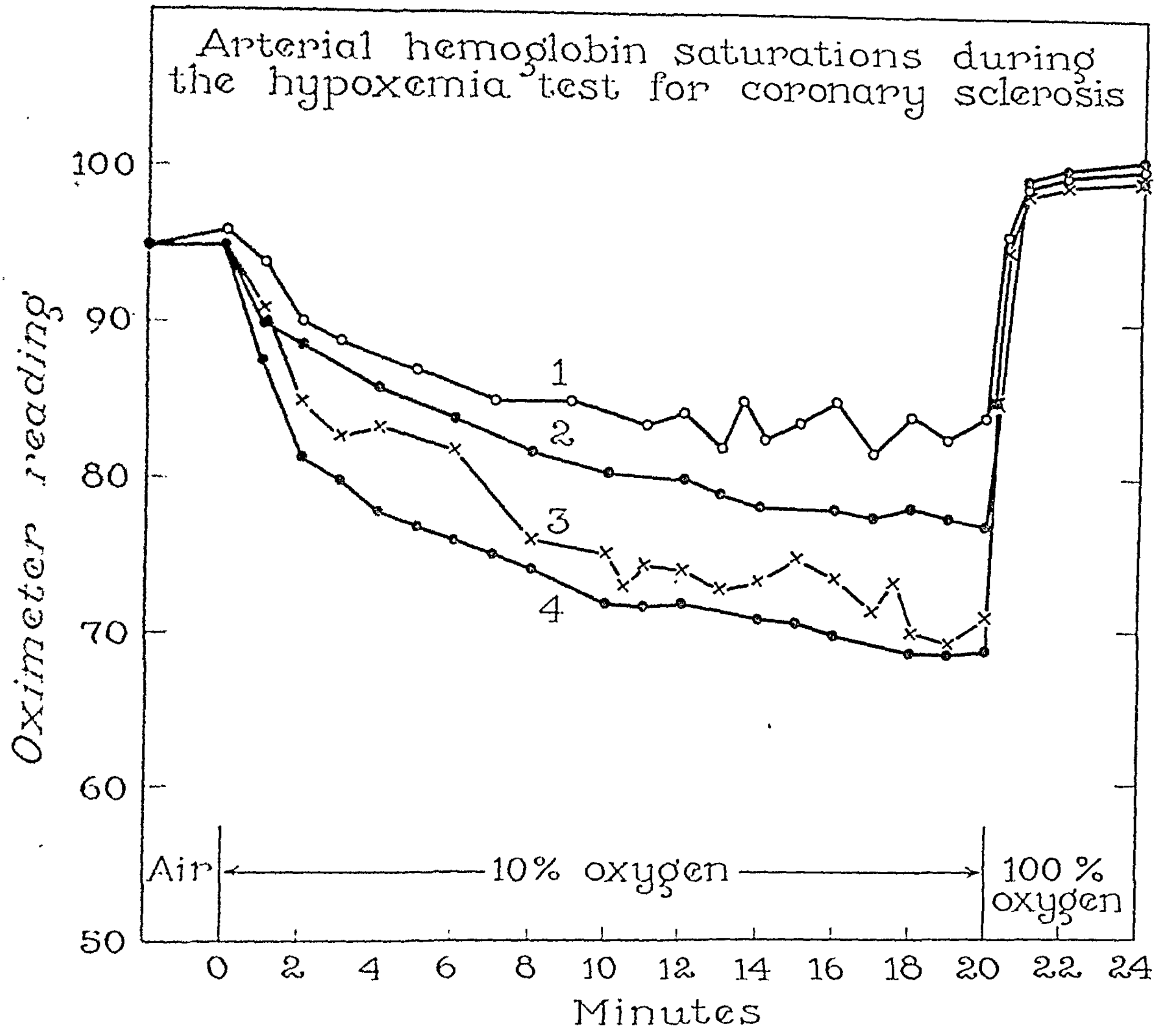

Fig. 1.—Oximeter readings on four patients during a twenty minute period in which 10 per cent oxygen was breathed. Cases were randomly taken to illustrate only the variation in the arterial saturation. The oximeter was arbitrarily adjusted to read 95 when air was being breathed, and in the four subjects shown, the reading became stabilized at 100 when 100 per cent oxygen was being breathed after the test. The ventilation rates and the ventilation per square meter of body surface for the four patients were, respectively: (1) 10.3 and 6.3 liters per minute, (2) 10.0 and 4.6 liters per minute, (3) 6.9 and 4.7 liters per minute, and (4) 8.0 and 4.25 liters per minute. The ventilation was measured for five minutes beginning at the end of the third minute of the test.

about the fourth to the tenth minute, which is followed by a second period of decrease in saturation readings. The values for arterial hemoglobin saturation obtained by this photoelectric method have seemed high but are not incompatible with values calculated from oxygen dissociation curves and alveolar gas equations, if increased pulmonary ventilation is assumed. However, from recent calibrations of our standard oximeters, it is suspected that the oximeter readings in the lower

scale were usually slightly higher than the true values for the arterial saturation. The volumes of expired gas, collected for a period of five minutes in twenty-three patients, and the values for arterial hemoglobin saturation at the end of the period, are shown in Fig. 2. Each sample was collected, beginning three minutes after the

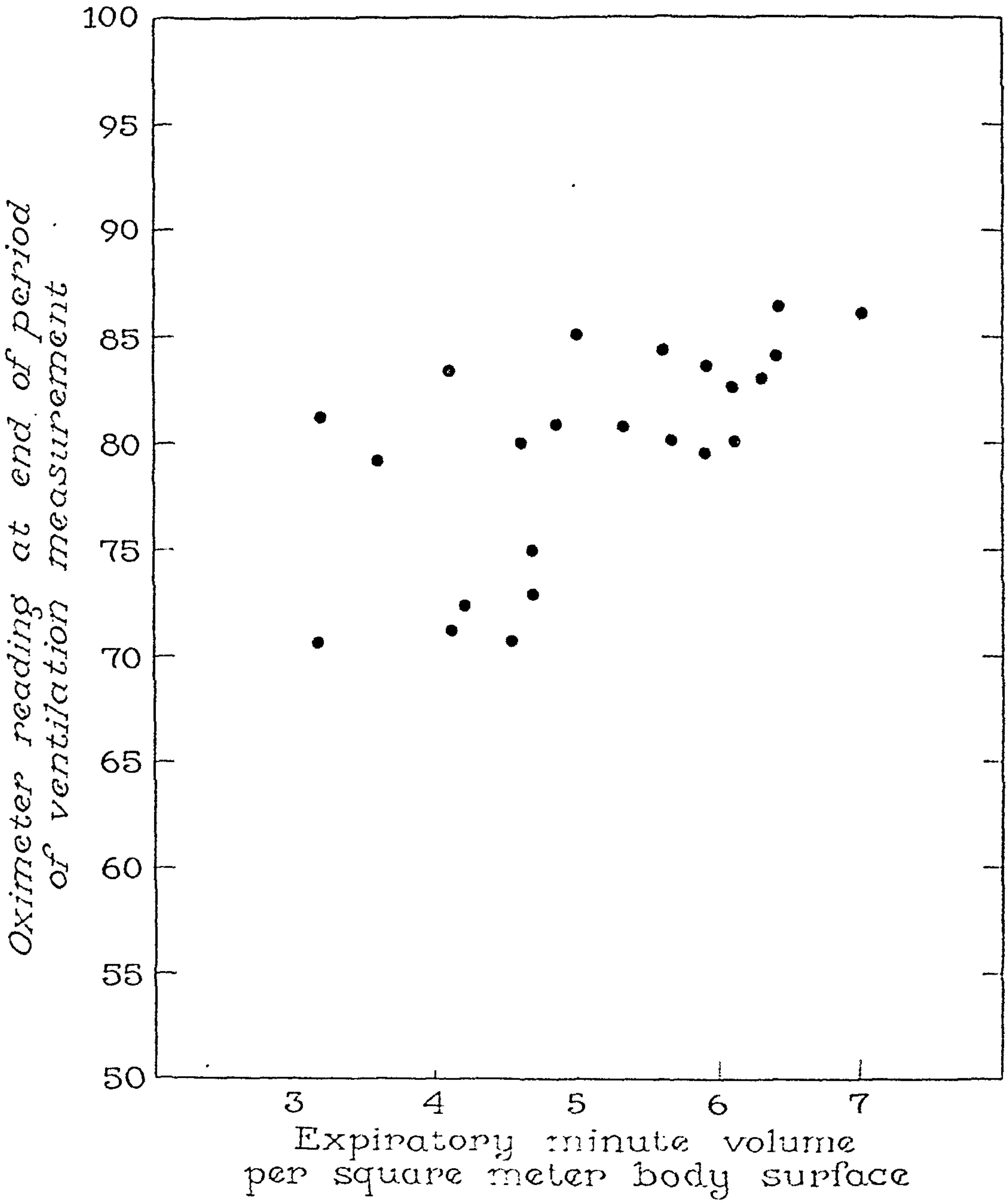

Fig. 2.—The relationship between oximeter readings and ventilation rate in twenty-three patients. The ventilation rate is expressed as the expiratory volume in liters, saturated at room temperature, per square meter of body surface. There is a trend for high oximeter readings to correlate with high expiratory minute volumes. When the actual measured volumes are charted, the scatter is even more marked.

subject had started breathing the oxygen-poor mixture, and was analyzed for content of oxygen and carbon dioxide. The respiratory quotients for pulmonary exchange were almost all greater than one. However, the figures for oxygen

consumption have not been considered entirely reliable. Absorption of nitrogen during this period would produce an error but not of the magnitude encountered. The imperfection in the measurement of oxygen consumption does not invalidate the measurement of ventilation. While there was a general trend for the oximeter reading at the end of the period of the collection of the expired gas (usually the end of the eighth minute of breathing the oxygen-poor mixture) to correlate with the ventilation rate, this relationship is not as direct as might have been expected. The scatter is practically as great when the ventilation is charted as a function of the surface area as when the actual ventilation volumes are charted. So far, we have not been able to obtain sufficiently reliable figures on oxygen consumption in the early period of the test to express the ventilation as a function of the oxygen absorbed.

The degree of desaturation of the arterial blood is not the critical determining factor in the production of a positive reaction to the test (Fig. 3). It is apparent

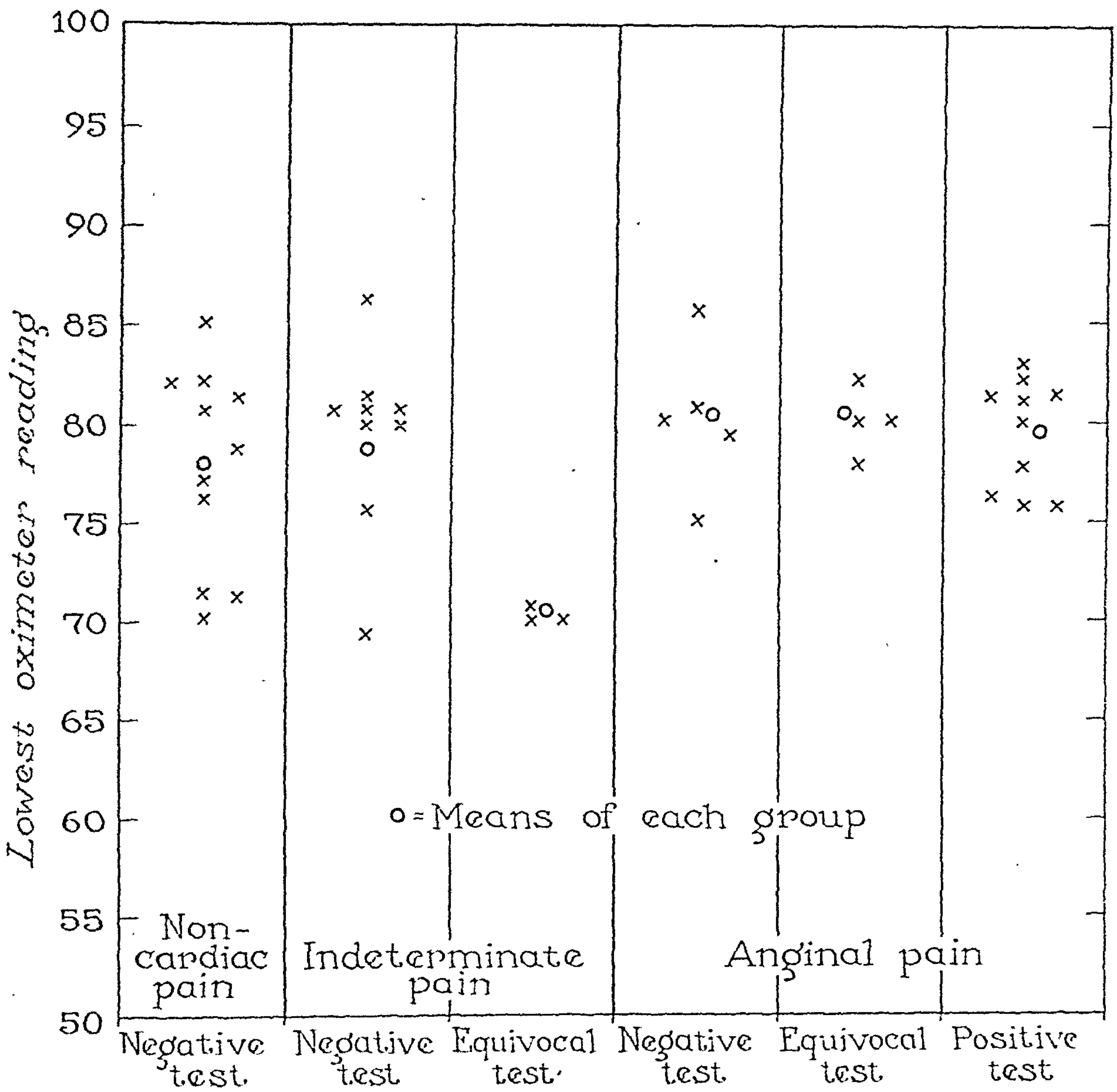

Fig. 3.—The relationship between the lowest oximeter reading during the hypoxemia test and a positive or negative electrocardiographic result.

that those patients having coronary sclerosis clinically and giving a negative reaction to the test had desaturation of a similar degree to that of patients giving positive reactions to the test. In the category of patients labelled as having indeterminate pain, it is believed that a considerable number had coronary sclerosis but the history was so atypical that the making of such a diagnosis was deferred. A few patients with similar atypical pain syndromes were, however, placed in the category of those with anginal pain after a positive reaction to the hypoxemia test was obtained.

(4) The main reason for the development of an area of injury seems to be best related to the inability of the stenotic coronary vessel to allow the tremendous increase of blood flow that normally takes place in anoxia. However, if such were the one and only factor it would be reasonable, perhaps, to assume that electrocardiographic evidence of localized myocardial ischemia would be seen more frequently. Significant evidence related to this problem may be derived from an analysis of the findings at necropsy in the only two cases in our series in which such data are available.

The one man was 43 years of age and gave a history of having had effort distress for ten years. On the first investigation he gave a negative reaction to the induced hypoxemia test. Three months later he experienced sudden thoracic pain while at rest and died in a few minutes. The heart weighed 410 grams, and there was no gross or histologic evidence of acute infarction. Severe atherosclerosis, Grade 3 of the left and Grade 2 of the right coronary artery, was present (graded on the basis of 1 to 4, in which 1 represents the least, and 4 the most severe condition). No acute occlusion was present.

The other patient was a man 50 years of age, who gave a history of having had effort distress for ten years. On the first investigation, he had marked diagnostic segment changes in his electrocardiogram during the hypoxemia test. He returned to the clinic seventeen months later and died suddenly. The heart weighed 530 grams, and there was no gross or histologic evidence of myocardial infarction. The atherosclerosis was graded 2 in the right coronary artery and 3 in both main branches of the left coronary artery. No occlusions were present.

Even from these two cases, which are quite similar in their clinical and pathologic characteristics, it is evident that the severity of the coronary sclerosis is not the sole factor determining whether the outcome of the hypoxemia test is positive or negative.

The evidence seems to indicate that factors of resistance to flow outside the structural limitation contribute to the myocardial ischemia. Among these factors may be those of (5) possible variations in the redistribution of the coronary flow and drainage and (6) the amount of coronary vasoconstriction. Some experimental work[5] has pointed to the importance of a relative acapnia as a contributing factor to the constriction, although the possibility of reflex vasoconstriction cannot be disregarded.

THE "POSITIVE" ELECTROCARDIOGRAM IN THE HYPOXEMIA TEST

As the studies on the hypoxemia test progressed, it was noted that the precordial leads were giving more information than the standard leads and that, indeed, they could be used practically exclusively, if desired. The typical and diagnostic changes in Lead CR_5 were marked depression (more than 2.0 mm.) of the RS-T junction and interval, or a frank reversal of the T wave. In a few instances, the T waves increased in height, a change which is believed to be of possible significance, and in two tests, which are to be discussed in greater detail later, an elevation of the S-T segment occurred.

The commonly occurring depression of the RS-T segment could be explained by a relative positivity of the ventricular cavity during systole. Among the ways this might be accomplished would be through injury of the endocardial layers of the heart, a state attended by incomplete depolarization of the constituent myo-

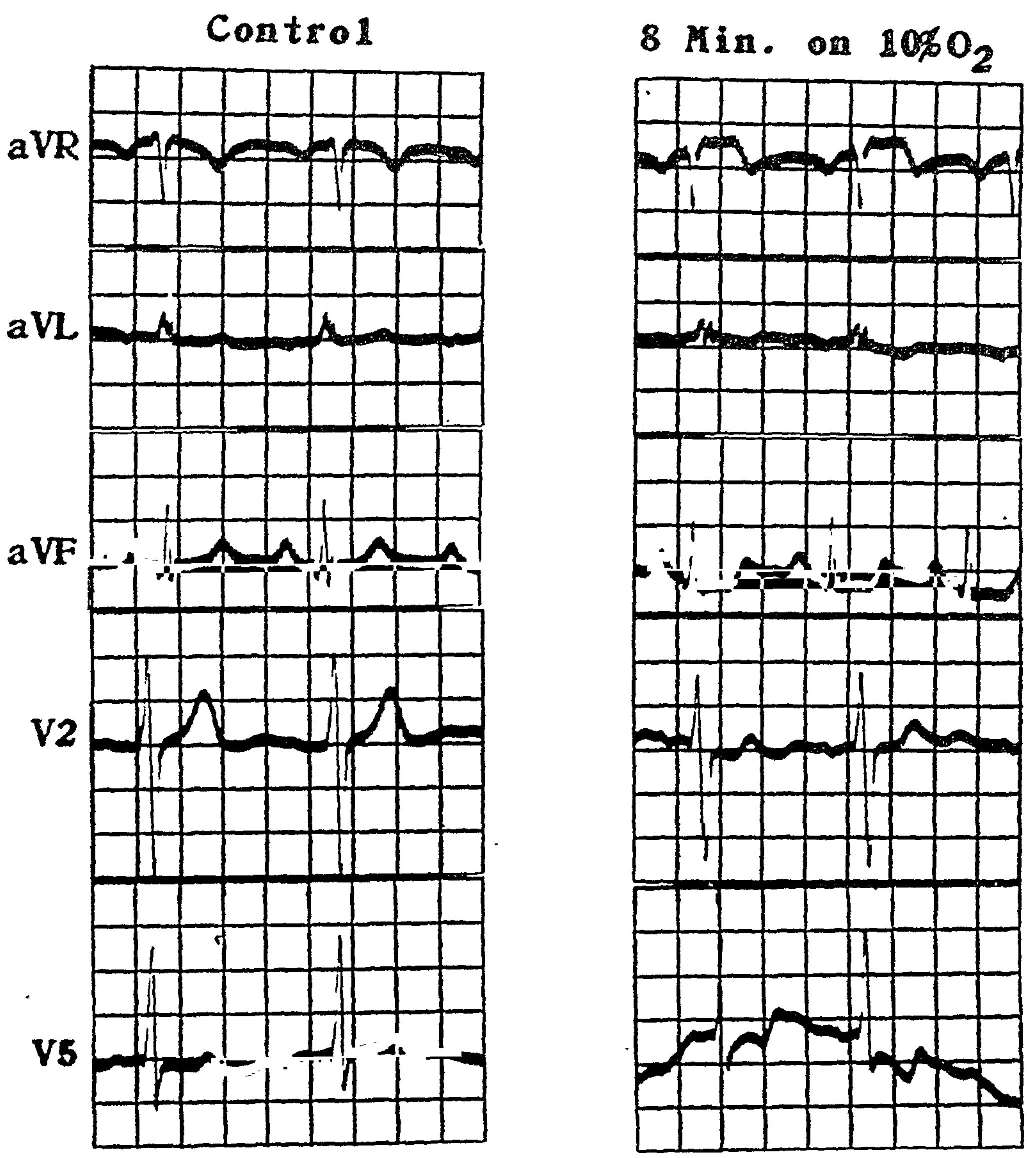

Fig. 4.—Electrocardiographic changes of a positive hypoxemia test with elevation of the S-T segment in the right arm unipolar lead and greatest depression of the S-T segment in the left leg unipolar lead and the apical precordial lead. The heart is in the electrocardiographic vertical position although the electrocardiographic orientation is not a classic type.

cardial cells. No matter what may be the basis of the electrophysical change, it was evident that certain significant data might be added to the information derived from the standard leads and a single precordial lead by measuring the potential differences between right arm, left arm, and left leg, respectively, and a relatively neutral terminal, and by exploring the thorax with multiple precordial leads. In the accompanying sets of electrocardiograms are illustrated certain results obtained by using these additional leads. In Fig. 4, a positive electrocardiographic result is seen with an S-T segment elevation in Lead aV_R

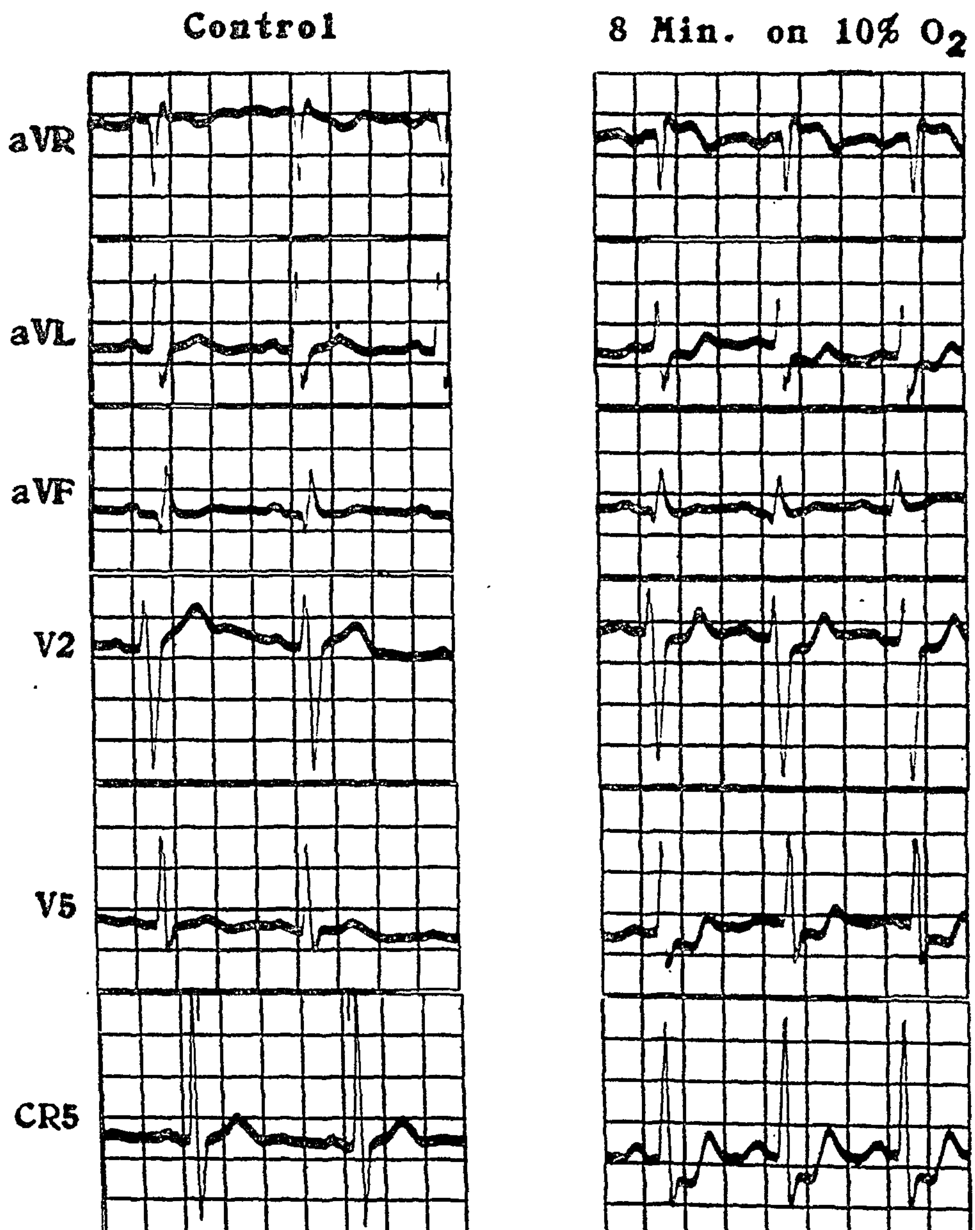

Fig. 5.—Electrocardiographic changes of a positive hypoxemia test with elevation of the S-T segment in the right arm unipolar lead and greatest depression of the S-T segment in the left arm unipolar lead and the apical precordial leads. The greater depression of the S-T segment in the precordial lead when the indifferent electrode was on the right arm instead of the central terminal (Wilson) is well demonstrated.

and S-T segment depressions in Leads aV_F and V_5 in an "electrocardiographically vertical" heart. In other tests, the segment depression was present in aV_L rather than aV_F; this finding occurs in the more "electrocardiographically transverse" heart (Fig. 5). In still other tests, the segment depression may occur about equally in Leads aV_L and aV_F. Evidence has accumulated which indicates that Lead aV_R reflects cavity potential.[8,9] Hence, there is reason to believe that with hypoxemia a potential difference exists across the ventricular wall with an additive manifest potential in the long axis of the left ventricle. An evident explanation for the observation that the segment change is greater in Lead CR_5 than in Lead V_5 exists in the fact that the right arm contributes to, and accentuates, the potential recorded in the former lead. The segment depression observed in the standard leads, usually maximal in Lead II but not infrequently in Lead I, may be similarly explained by the ventricular position.

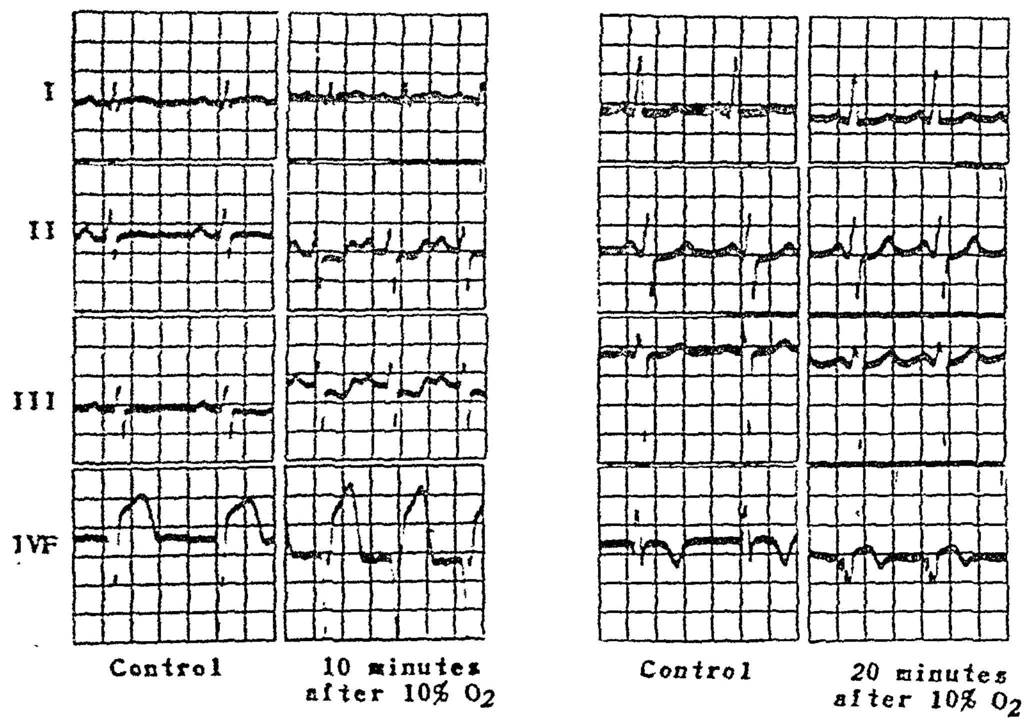

Fig. 6.—The electrocardiographic changes of two patients with hypoxemia who had had a previous anterior myocardial infarction as indicated by the control thoracic leads. The elevation of the S-T segment in the precordial lead is of especial interest and is discussed in the text. The change in the QRS complex of the precordial lead in the tracings on the right may be related to a different orientation of the myocardial scar to the thoracic wall and precordial electrode.

Early in our experience with the procedure, three patients were given the test who had had ancient myocardial infarctions which, before the test was given, had gone unrecognized because of inadequate precordial leads. It is noteworthy that these patients had, in the precordial leads, electrocardiographic changes which were opposite to those of the other patients with electrocardiographically positive reactions to the test. The segment elevation in the precordial lead, with a Q wave and absent R, is a striking effect (Fig. 6). If in explanation of these changes the window theory is utilized, cavity potential is being tapped through the myocardial scar. The results then became compatible with our previous

theoretical discussion. Similar S-T elevations in precordial electrocardiograms in which there was evidence of old anterior apical infarction have been observed by Holzmann[10] in connection with the exercise test.

The reversal of the T wave from a normal positive is rather infrequent and can be explained on the basis of ischemia of the myocardium. Perhaps more interesting theoretically is the reversal of an inverted to an upright T wave. In

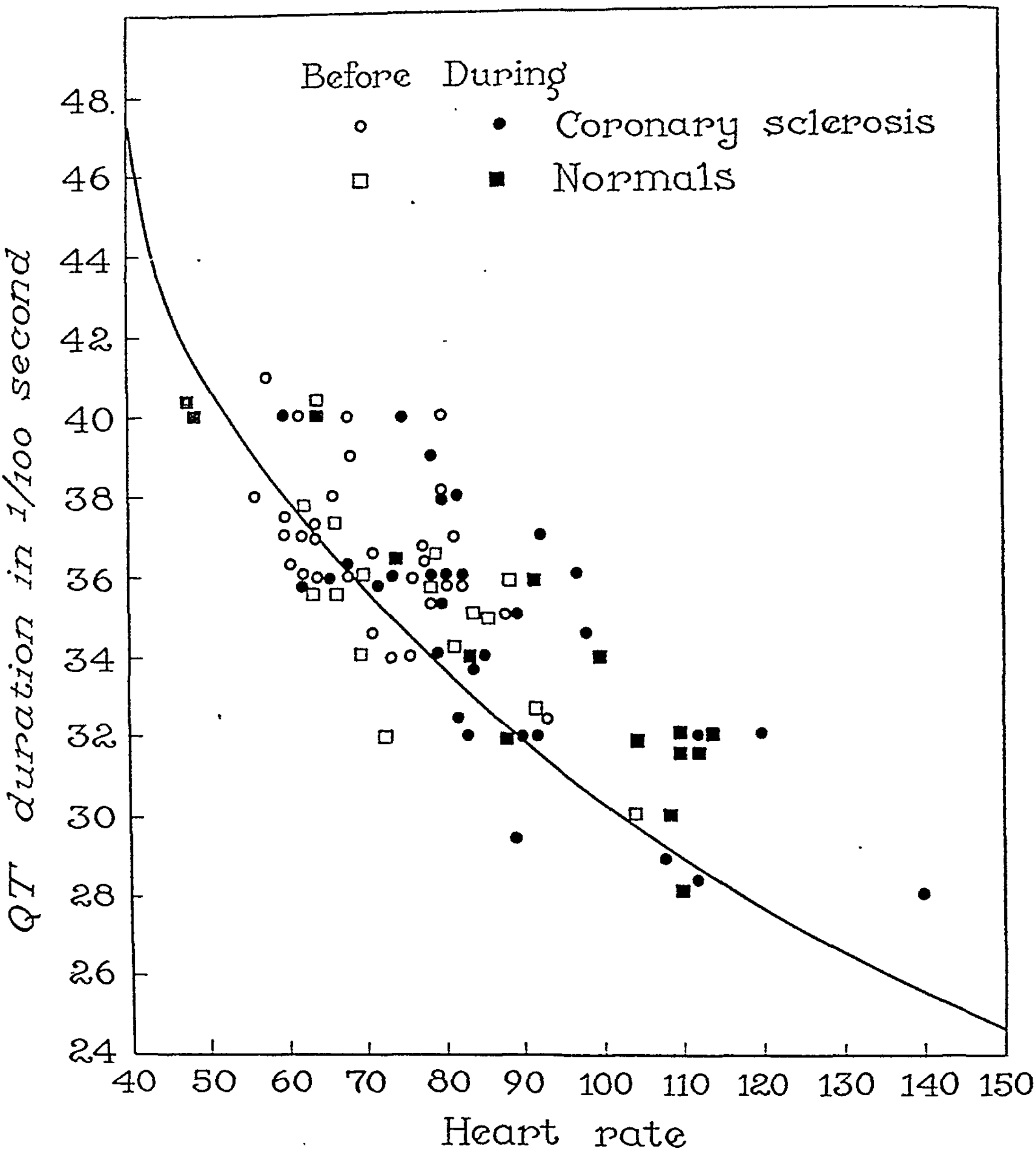

Fig. 7.—The Q-T intervals before and after twenty minutes of hypoxemia in fifteen patients without heart disease ("normals"), fifteen patients with coronary sclerosis and a negative reaction to the test on electrocardiographic examination, and fifteen patients with coronary sclerosis and a positive reaction to the test on electrocardiographic examination. In the majority of instances the Q-T interval shortens or lengthens with the increase or decrease in cardiac rate following a normal relationship. In two patients with coronary sclerosis and a negative reaction to the test, there was an absolute increase in Q-T duration in spite of moderate tachycardia, the significance of which is not known. The change in heart rates may be noted to be slight to moderate. The line representing the mean values for Q-T intervals in relationship to heart rate is taken from Koch's[14] "Allegemeine Elektrokardiographie."

addition to these changes, one occasionally sees increased voltage of the precordial T wave, a reversal of the usual change with hypoxemia; this is believed to be an alteration suggestive of coronary insufficiency.[2]

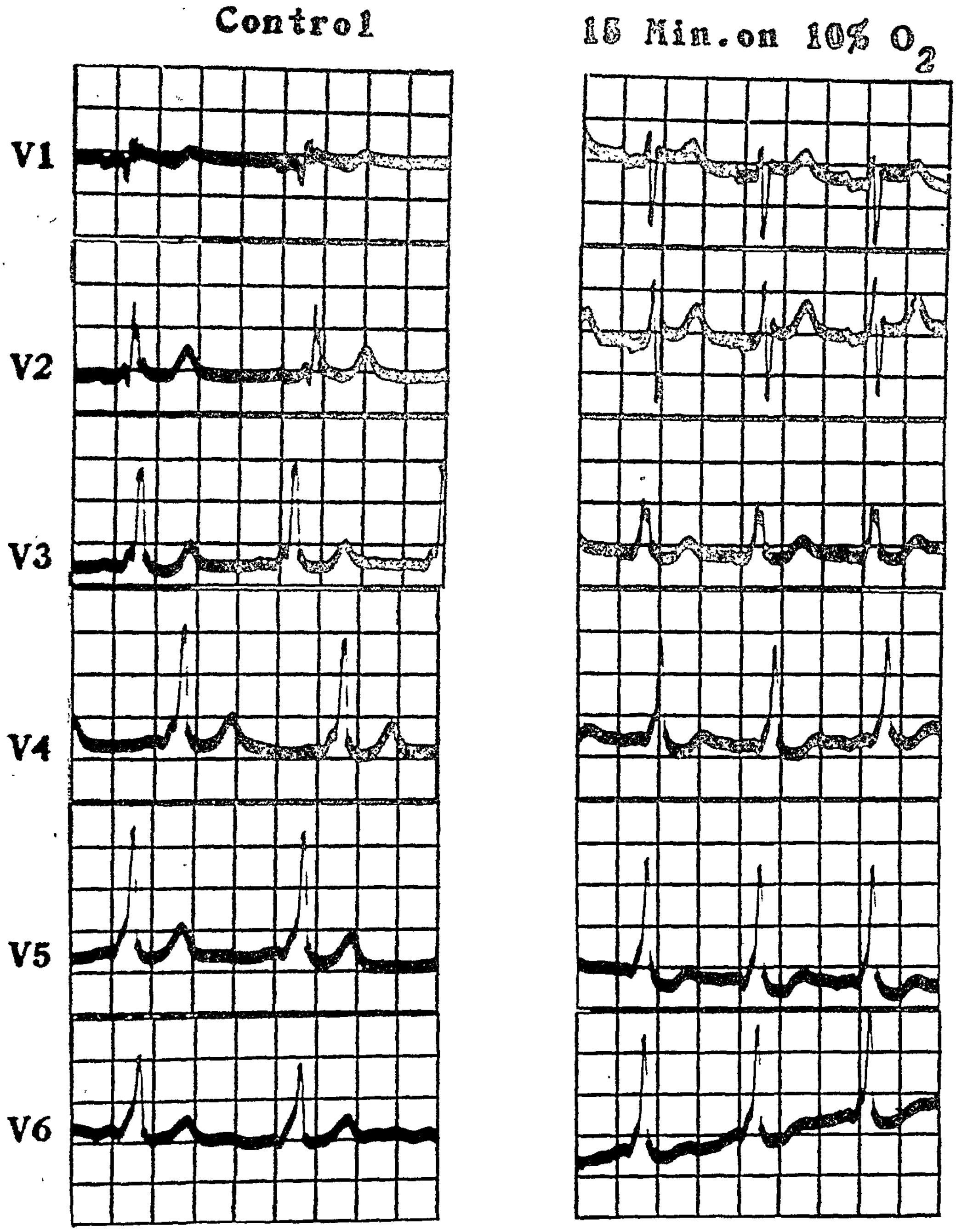

Fig. 8.—Electrocardiograms of the Wolff-Parkinson-White syndrome type in a patient suspected of having coronary insufficiency. Two hypoxemia tests two years apart showed identical changes but the interpretation is difficult. While the electrocardiographic changes observed during the period of hypoxemia are considered to be supportive of the diagnosis of coronary sclerosis, the diagnosis from both clinical and electrocardiographic viewpoints has been deferred.

A change in the duration of the P-R, QRS, or Q-T intervals of degree sufficient to be of value in the interpretation of the test has rarely occurred. In one case, left branch block developed during the period of induced hypoxemia but later an intermittent block was observed to occur frequently without any change in the patient's environment. The Q-T intervals usually follow the normal

relationship to the cycle length but, in rare instances, persons with coronary sclerosis showed an opposite relationship, with the Q-T interval increasing to the upper limit of normal (Fig. 7). This has happened with and without other changes in the electrocardiogram. As there is some evidence[11] to indicate that the systolic index in normal persons under hypoxic conditions first shortens and then greatly lengthens as the subject approaches a state of collapse, further doubt should be entertained as to the dependence of Q-T changes upon the presence of coronary insufficiency during the test.

In an occasional patient, ventricular extrasystoles appeared during the test and, if these were frequent, the procedure was terminated. The significance of the appearance of such an arrhythmia is unknown but it has been assumed that it might create an increased hazard.

When the control electrocardiograms have shown abnormalities of any type, we have been hesitant to interpret further moderate changes which occurred during hypoxemia as evidence of coronary insufficiency. Our experience is quite small in such a group, as patients with ventricular hypertrophy, those taking digitalis and those with definite electrocardiographic deviations from normal, do not require a hypoxemia test for diagnosis. The problem, however, is illustrated by a patient having the Wolff-Parkinson-White syndrome and atypical thoracic pain (Fig. 8). The electrocardiograms made during the hypoxemic stress show changes, but these changes are not beyond the range of abnormality that may exist in this syndrome without such stress.

FOLLOW-UP STUDY ON PATIENTS WHO HAD HAD THE HYPOXEMIA TEST

An attempt was made to obtain information on the patients who had been given the hypoxemia test for coronary insufficiency during the first three years it was used, allowing follow-up periods of three to six years. Questionnaires were sent to 300 patients and reports were obtained concerning 204. Of these 204 patients traced, twelve were not considered further because they had had an unsatisfactory hypoxemia test; thirty were dead and there was presumptive or definite evidence that each death was related to coronary insufficiency (Table I).

TABLE I. DATA ON TWO HUNDRED AND EIGHTY-EIGHT PATIENTS THREE TO SIX YEARS AFTER A SATISFACTORY INDUCED HYPOXEMIA TEST FOR THE DIAGNOSIS OF CORONARY SCLEROSIS

CLINICAL DIAGNOSIS AND RESULT OF HYPOXEMIA TEST	PATIENTS		CONDITION			NOT TRACED
	TOTAL	TRACED	SAME OR IMPROVED	WORSE	PATIENTS DEAD	
Angina pectoris, positive test	86	57	30	11	16	29
Angina pectoris, negative test	45	33	17	10	6	12
Possible anginal syndrome, negative test	56	39	26	6	7	17
Noncardiac thoracic distress, negative test	101	63	57	5	1	38
Total	288	192	130	32	30	96

The average age of the group of thirty patients who died was 47 years, with a range of from 35 to 60 years. The average duration of life after the test in this group was eighteen months, with a range of from three days to forty-four months.

Of this group of thirty patients, *nine* had normal control tracings and a pain response; of these nine, seven had positive and two had equivocal results in the electrocardiographic study. Of twelve patients with normal control electrocardiograms and marked diagnostic electrocardiographic changes with hypoxemia, seven had pain (Table II). The data might be interpreted as indicating that pain due to true coronary insufficiency is practically always associated with some electrocardiographic changes of the ischemic type but that such electrocardiographic changes frequently occur in hypoxemia without anginal pain.

TABLE II. DATA CONCERNING THIRTY PATIENTS WHO UNDERWENT A SATISFACTORY INDUCED HYPOXEMIA TEST AND LATER DIED OF CORONARY INSUFFICIENCY

CONTROL ECG	TOTAL	RESULT OF TEST				PAIN
		POSITIVE	EQUIVOCAL	NEGATIVE	UNSATISFACTORY	
Normal (including left axis deviation)	20	12	3	4	1	9
Right axis deviation	1	0	0	1	0	1
Right bundle-branch block	1	0	0	1	0	1
Negative or diphasic T_4	4	1	1	2	0	1
Absent R_4, negative T_4	3	1	2	0	0	2
Left axis deviation and digitalis	1	1	0	0	0	0
Total	30	15	6	8	1	14

COMMENT

The experience gained from the performance of approximately 730 induced hypoxemia tests for the diagnosis of coronary sclerosis after the method of Levy has reaffirmed our previous views as to the clinical value of the test. In selected cases the test has been of great assistance in the diagnosis of coronary insufficiency, and when coronary sclerosis of clinical magnitude is present, one may expect a positive result in about 50 per cent of cases. There has been an understandable tendency sometimes to employ the procedure as an exclusion test; one must constantly be on guard to avoid such an error. Among the patients who have been studied are a large number of physicians, young patients with essential hyperlipemia, and patients with diaphragmatic hernias. In the last group of cases, the test has not infrequently supported the clinical impression that symptoms were related to coronary insufficiency and not directly to the hernia. So far, it has been impossible to ascertain the degree of coronary disease that must be present before a positive reaction to the test is obtained, but it is known that severe sclerosis may be present with a negative reaction.

The continuous study of the arterial saturation throughout the test has added to our knowledge of the physiologic stress imposed, but otherwise it has

been of only slight help in the interpretation of the results. Positive results have been obtained both with the low and the fairly high arterial hemoglobin saturations. One gains some knowledge of the ventilatory function during the test so that one can caution the patient against excessive ventilation. When saturation values have fallen to less than 75 per cent, and particularly to 70 per cent, our attention to the patient's condition has been further alerted and such a low saturation has not been allowed to continue for more than a few minutes. For the routine test, the incorporation of the oximeter is not necessary, although the only disadvantage to the use of the oximeter has been the longer control period that is required to permit proper equilibration of the instrument.

One may emphasize again the precautions which must be observed in order that the test may be called a safe clinical procedure. First, in the selection of the patients the following persons should be excluded: those who are more than 60 years old, those with obviously enlarged hearts, those with previous myocardial infarction, those with pulmonary disease, such as emphysema, and those who are generally ill. Secondly, the physician who has some familiarity with the patient's symptoms should personally supervise the test. The knowledge that death from anoxia can occur at relatively low altitudes[12] has not caused decrease in one's respect for the severity of the stress imposed by the hypoxemia test. However, the short time the patient is exposed to low oxygen tensions undoubtedly constitutes an important safety factor.

Our opinion as to the increased stress imposed upon the subject when the test is performed in localities at higher altitudes than that of Rochester has not changed since our first report. The stress is increased, but partial protection is present through the normal acclimatization to altitude. It is believed that the choice of a 10 per cent oxygen mixture was a fortunate one, and at this time we would doubt the wisdom of using a lower percentage.

Our studies with special electrocardiographic leads, namely, the unipolar extremity leads which have been routinely used in the test for eighteen months, have elucidated the genesis of the electrocardiographic pattern but have not contributed significantly to the evaluation of a positive or negative electrocardiographic test. Our electrocardiographic interpretations support the theory that a gradient of injury, increasing toward the endocardium, exists, which is consistent with the theory of injury discussed by Johnston and Wilson.[13] As the interpretation of the test is based on the quantitation of the electrocardiographic changes, it is expedient to use leads where these changes are summated. For this reason the CR leads have certain advantages in the routine tests.

SUMMARY AND CONCLUSIONS

1. The various factors that may contribute to the stress imposed on the heart in coronary sclerosis by the breathing of a mixture of 10 per cent oxygen in nitrogen are discussed. Two cases are cited to indicate that a similar severe degree of coronary sclerosis may be present in patients with a negative or positive reaction to the test. The conclusion is drawn that, in many cases, coronary vasoconstriction is an important factor in determining whether an area of injury develops within the myocardium.

2. In practically all patients, increased ventilation occurs and apparently there is a rough correlation between the extent of increase in ventilation and the degree of arterial hemoglobin saturation.

3. The degree of arterial hemoglobin saturation is not the main factor which determines whether a positive or negative reaction to the test occurs in persons with coronary sclerosis. A physiologically unsteady state is present throughout the whole period of the induced hypoxemia and comparisons cannot be justly made to determinations wherein equilibrium has been established. The brief duration of the test is a safety factor. It is believed that the period of exposure to low oxygen tension may be shortened from twenty minutes to fifteen minutes without significantly reducing the percentage of positive results.

4. Patients with moderate hypertension and cardiac enlargement apparently give a positive reaction to the test only if coronary insufficiency related to coronary sclerosis is also present.

5. The electrocardiographic changes follow a pattern which is consistent with, and supportive of, the concepts of the dipole theory as they are related to a myocardial injury wherein the more seriously affected cells lie in the endocardial layer.

6. The disturbed myocardial state giving rise to the electrocardiographic changes during the test may exist independently of the physiologic stimulus for pain.

7. Patients with coronary sclerosis and a positive reaction to the test have as good a prognosis as those with a negative reaction.

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MYOCARDITIS ASSOCIATED WITH ACUTE AND SUBACUTE GLOMERULONEPHRITIS

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MYOCARDIAL failure has been recognized as a possible concomitant of acute glomerulonephritis for some time. Goodhart[1] (1879) was probably the first to implicate the heart muscle as the cause of cardiac failure in this condition. He reported fatalities in six children in whom nephritis had developed subsequent to scarlet fever; two of the deaths were unexpected. Autopsy examinations were made in five, disclosing a dilated heart in each instance; there were no microscopic studies. Master and co-workers[2] stated that myocardial insufficiency is common in patients with acute glomerulonephritis and may at times be severe enough to cause death; they found it in eight of the twenty-four patients they studied. They related cardiac functional impairment to actual myocardial damage and not to left ventricular exhaustion from suddenly increased peripheral resistance. Impressed by the paucity of significant anatomic changes in the routine heart sections examined (one autopsy from their series and six others), they suggested that the profound changes in the blood and tissue electrolytes altered capillary permeability, which, in turn, caused myocardial damage. Nonetheless, their report includes one instance of serous myocarditis and several of edema of the musculature of the heart. Whitehill and associates[3] found that 71 per cent of their series of 138 patients with acute nephritis showed clinical evidence of cardiac insufficiency; however, these authors expressed the opinion that microscopically the heart muscle was "almost universally reported as being normal, or at the best slightly edematous." They also found that the incidence of myocardial failure encountered varied in direct proportion to the severity of the nephritis. Proger,[4] impressed by the failure to find significant lesions in the myocardium, postulated that the clinical manifestations commonly thought to be indicative of left ventricular failure in myocarditis were in reality evidence of an increase in the pulmonary blood volume produced by some unspecified extracardiac mechanism.

Failure to find appreciable morphologic change in the heart was not universal. Darrow,[5] describing the heart muscle in a fatal case of acute nephritis following scarlet fever, reported that the bundles were spread apart as if by fluid, and noted perivascular accumulations and diffuse subendocardial infiltrations of

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mononuclear cells; he noted also a few plasma cells, but no polymorphonuclear leucocytes. No conclusions as to etiological factors could be drawn because of the antecedent scarlet fever. Three cases of myocarditis with acute nephritis were included in the review by Saphir,[6] but a brief survey of the literature indicates a lack of adequate pathologic data to explain this frequent functional disturbance.

MATERIAL

During a review of the material available at the Army Institute of Pathology a number of cases were found in which myocarditis was associated with acute and subacute glomerulonephritis. Excluding cases of acute nephritis occurring subsequent to illnesses such as scarlet fever, typhus fever, or septicemia (which in themselves may produce significant myocardial changes), this complication was found in sixteen of 160 fatal cases of acute and subacute glomerulonephritis. The information gathered from the records and from examinations of prepared slides from these cases form the substance of this report. All sixteen patients were men. Their ages ranged from 20 to 49 years, but most were between 20 and 30 years of age. All of them presented the characteristic clinical manifestations of acute glomerulonephritis. Often the history of an acute infection of the upper respiratory tract preceded the onset of renal disturbances, and one patient was known to have had an acute antecedent pyogenic infection of the skin.

CLINICAL OBSERVATIONS

The majority of the fatalities in the cases of glomerulonephritis were attributable to heart failure. This condition was recognized clinically in six patients (Cases 2, 4, 8, 9, 10, and 16) but not in six others, although the records included similar clinical observations. In two additional cases the recorded evidence of myocardial failure was limited to the rapid development of pulmonary edema in one and a striking disproportion of pulse and temperature (90 per minute and 104°F) in the other. The two remaining patients died of bronchopneumonia and renal insufficiency, respectively.

There were four unexpected deaths; however, these patients had shown various manifestations of heart failure. The signs and symptoms regarded as indicative of impaired cardiac function were as follows: cyanosis and dyspnea, which occurred in eleven patients; disturbances of rhythm in fourteen (tachycardia in ten, gallop rhythm in three, and auricular fibrillation in one); bradycardia (relative to the temperature) in five; hypotension in three; a weak, thready pulse in two; and ankle edema unassociated with facial edema in two. Electrocardiographic tracings were available for four patients and were abnormal in three. Cheyne-Stokes respiration occurred once. Six of the patients were given sulfonamides and five, penicillin; eight received fluids intravenously. Tables and brief clinical synopses are included to facilitate clinicopathologic correlations (Table I).

TABLE I. CLINICAL MANIFESTATIONS OF MYOCARDITIS ASSOCIATED WITH ACUTE AND SUBACUTE GLOMERULONEPHRITIS

MANIFESTATION	CASES IN WHICH MANIFESTATION OCCURRED
Cyanosis	1, 4, 7, 8, 10, 11, and 13
Dyspnea and/or orthopnea	1, 2, 4, 5, 6, 7, 8, 9, 11, and 13
Cheyne-Stokes respiration	11
Tachycardia	1, 2, 3, 4, 7, 8, 10, 11, 13, and 14
Relative bradycardia	5, 6, 7, 15, and 16
Gallop rhythm	1, 2, and 8
Auricular fibrillation	16
Abnormal electrocardiograms*	2, 4, and 16
Unexpected deaths	2, 3, 4, and 9
Hypotension and/or weak pulse	1, 4, 7, 11, and 15
Precordial pain	7 and 9

*The only other electrocardiogram recorded was normal (Case 15).

PATHOLOGIC OBSERVATIONS

Gross.—At autopsy the viscera of all subjects exhibited passive hyperemia. Marked pulmonary edema had occurred in eight; in thirteen there were accumulations of fluid in the serous spaces. Unrelated pathologic findings included bronchopneumonia in nine, small pulmonary infarcts in the presence of a fractured leg in one, and purpuric manifestations in another.

The kidneys were uniformly enlarged and increased in weight; most of them were red and congested, but pallor was noted in a few. The histologic appearance of all sixteen corresponded to Bell's[7] description of the condition he has designated diffuse proliferative glomerulonephritis. Eleven had the histologic characteristics of acute intracapillary nephritis. In one additional case in which sulfonamides were used, there was a superimposed distal nephron nephrosis. The remaining cases showed sufficient additional changes to warrant classification as subacute nephritis in two and acute to subacute nephritis in two instances.

The hearts were usually increased in weight: three weighed 500 grams; seven, between 400 and 500 grams; two, between 300 and 400 grams; and two were considered of normal weight: 250 grams and 270 grams, respectively. Qualitative alterations described in twelve hearts included dilatation in nine and grossly recognizable changes in the myocardium in eight. Such changes included softening of the myocardium, or pallor, mottling, or streaking of the heart muscle. Table II summarizes these data.

Microscopic.—As in other forms of myocarditis the distribution of the lesions was patchy and not all areas of the musculature were equally involved. There was no evident predilection for or special vulnerability of any part of the heart. The process was mainly of the interstitial type, and evidence of muscle necrosis or destruction was rare and inconspicuous (Figs. 1 through 7). Diffuse infiltrates of inflammatory cells were never observed; on the contrary, the inflammatory foci were small and involved only portions of a section. The serous component of the exudate was particularly conspicuous; the interstitial tissues were loosened by

Table II. Myocarditis Associated With Acute and Subacute Glomerulonephritis

Case	Duration in Days	Acute Antecedent Respiratory Infection	Clinical Evidence of Heart Disease	Blood Pressure	Blood Nitrogen Mg. per cent	Sulfa Medication	Intravenous Fluids	Pulmonary Edema	Serous Effusions	Bronchopneumonia	Other Complications	Heart Weight in Grams	Cardiac Dilatation	Gross Abnormalities of Myocardium	Type of Nephritis
1	8	+	+	—	—	0	0	+	+	0	0	270	+	+	Acute
2	10	+	+	144/90	Normal	0	+	0	+	+	0	450	+	+	Acute
3	10	0	+	118/70	N.P.N. 195	0	0	+	+	0	0	500	+	0	Acute
4	12	+	+	132/76	B.U.N. 36	+	+	0	+	⊕	Infected chest wound	500	0	0	Acute†
5	13	0	?	—	—	0	+	+	0	0	0	430	—	—	Subacute
6	14	+	+	200/90	—	0	0	+	0	0	0	454	0	+	Acute
7	16	+	+	90/40	N.P.N. 45-120	+	+	0	+	+	0	411	+	+	Acute
8	17	+	+	136/86	—	+	0	0	+	+	0	425	+	0	Acute
9	18	0	+	158/100	B.U.N. 21	0	0	+	+	0	0	450	+	0	Acute
10	19	—	+	135/80	—	0	0	+	+	0	0	450	+	+	Acute
11	19	+	+	90/64	N.P.N. 214	+	+	0	0	⊕	0	Grossly normal			Acute-subacute
12	20	+	0	170/100	N.P.N. 120	+	+	+	+	+	0	379	0	0	Subacute
13	30	+	+	Elev.	—	+	—	0	+	+	Pulmonary infarcts	500	+	0	Acute
14	38	+*	0	112/72	N.P.N. 35	+	0	0	+	⊕	Purpura	250	0	+	Acute
15	38	0	?	100/54	B.U.N. 60-75	0	+	+	+	0	0	340	+	+	Acute
16	53	+	+	138/80	Normal	0	+	0	+	+	Pericarditis	—	—	+	Acute-subacute

*Also an acute pyogenic skin infection one month previously.
†Additionally there was a distal nephron nephrosis.
⊕ Streptococcal bronchopneumonia.

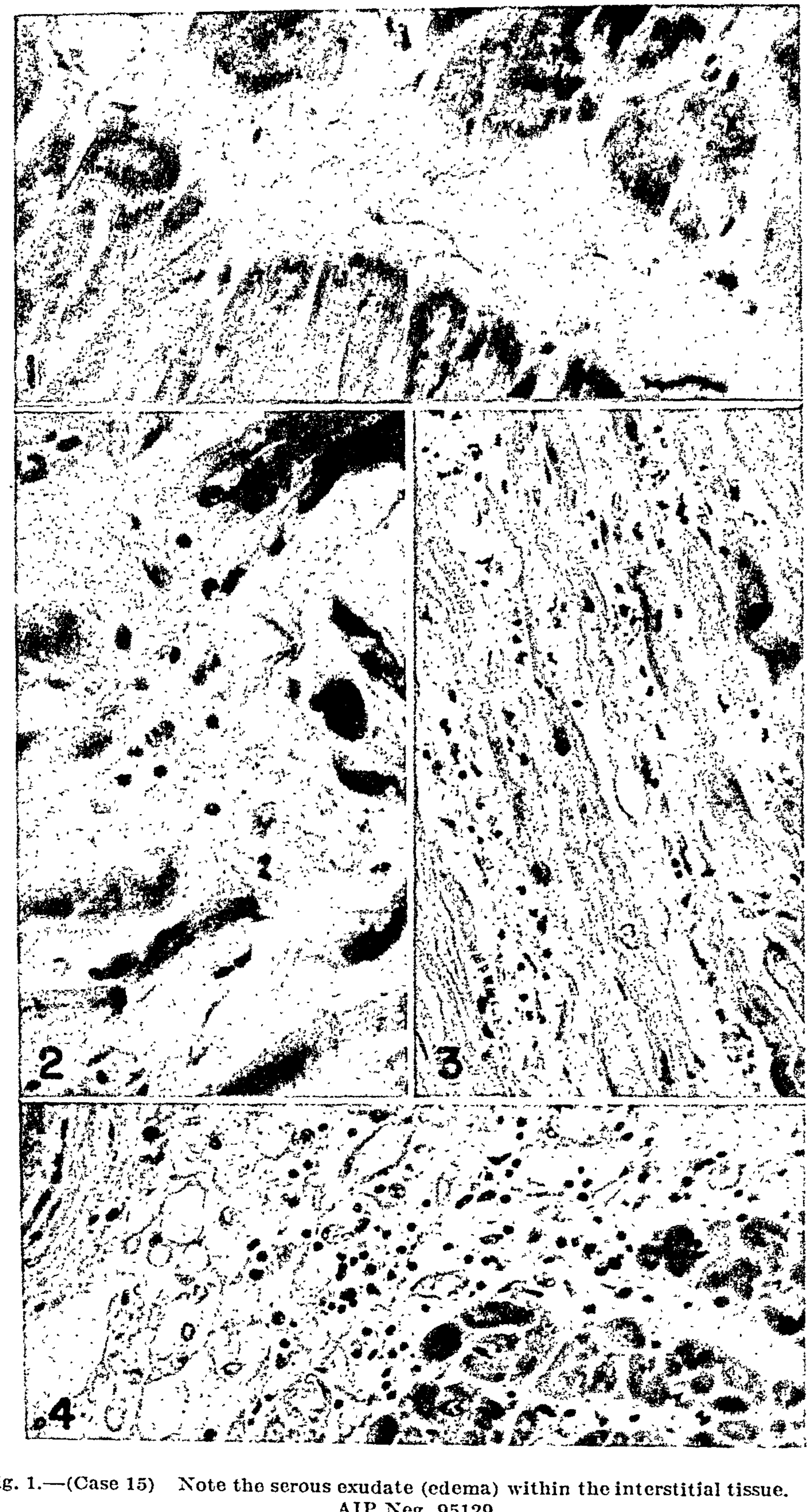

Fig. 1.—(Case 15) Note the serous exudate (edema) within the interstitial tissue. ×435 AIP Neg. 95129.

Fig. 2.—(Case 15) Note the spreading of the muscle fibers by the serous exudate and the very few cellular elements. ×470 AIP Neg. 95119.

Fig. 3.—(Case 15) Note the thinned-out muscle fibers, the serous exudate, and the presence of a predominantly lymphocytic infiltrate. ×315 AIP Neg. 95122.

Fig. 4.—(Case 15) Lymphocytes and a few endothelial leucocytes form the cells of the exudate. ×315 AIP Neg. 95130.

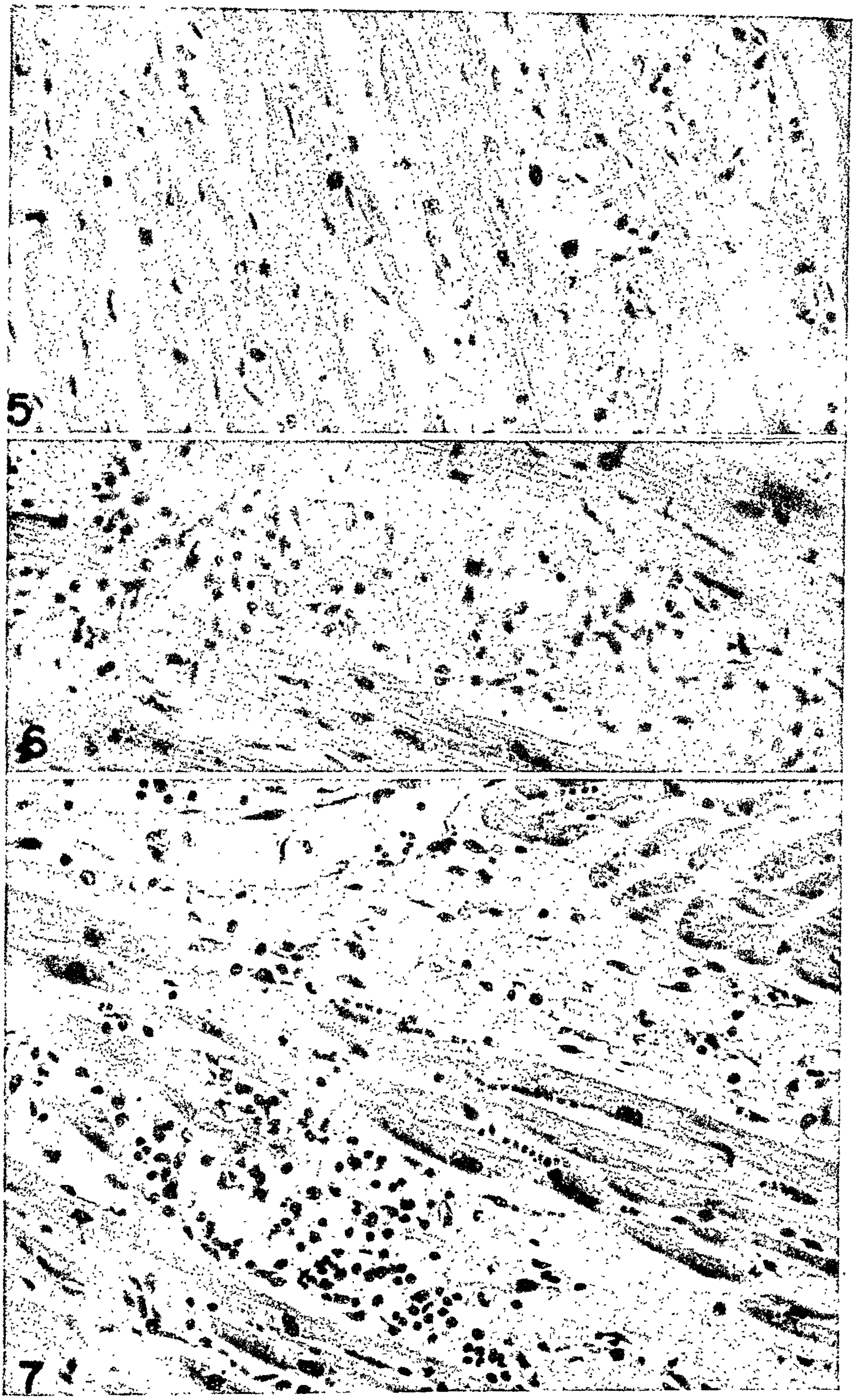

Fig. 5.—(Case 14) A few Aschoff cells and lymphocytes predominate. The muscle fibers are spread by the serous exudate. ×315 AIP Neg. 95110.

Fig. 6.—(Case 9) Many lymphocytes are present, principally in the interstitial spaces, but also tending to displace muscle fibers. ×315 AIP Neg. 95123.

Fig. 7.—(Case 10) Note the many endothelial leucocytes. ×315 AIP Neg. 95112.

the presence of a faintly eosinophilic fluid which dispersed the muscle fibers (Figs. 1 and 2). A small number of inflammatory cells were scattered through the fluid. The proportionate distribution of cells encountered varied from one area to another; lymphocytes and endothelial cells formed the usual and predominant types (Figs. 3 and 4), but Aschoff cells* were often present and, with endothelial cells, sometimes formed the principal cellular elements (Figs. 5 and 6). The occasional eosinophils and mast cells noted did not seem to be an essential part of the exudate. Polymorphonuclear leucocytes were generally absent and there were no structures which could be identified with, or mistaken for Aschoff bodies. The muscle fibers were the seat of varying degrees of cloudy swelling.

DISCUSSION

Considering the high incidence of cardiac insufficiency found clinically in acute glomerulonephritis, we have reported relatively few instances of myocarditis. Our figure, 10 per cent of 160 cases, contrasts sharply with 71 per cent of 138 cases reported by Whitehill and associates,[3] and differs significantly from the 17 to 40 per cent incidence found by various other authors whom they cite. The discrepancy is more apparent than real. Mention has already been made of the patchy distribution of the inflammatory changes in the heart muscle. It is reasonable to assume that in some instances myocarditis was overlooked because the examination of the heart muscle was not sufficiently thorough. The routine sections of myocardium examined in this study constitute but a minute sample of the cardiac musculature.

In consideration of the pathogenesis of the myocardial lesions encountered in these cases of acute nephritis, it is mandatory to evalute the effects of the antecedent infection upon the heart muscle. In another study we have described myocarditis which developed as a result of, or in association with acute infections of the upper respiratory tract. Such illnesses preceded the onset of nephritis in eleven cases of this series. Whitehill and his associates[3] reported that the "onset of nephritis was preceded in about 80 per cent of the [138] patients by more or less severe infections of the tonsils or respiratory tract." As already stated, the type of myocarditis associated with acute glomerulonephritis was characteristically serous, an observation made in those cases both with and without history of recent acute infection. This feature distinguished it from the much more cellular reaction observed in the form of myocarditis associated with acute nasopharyngeal and tonsillar infections. In the latter, too, significant degrees (moderate or marked) of muscle necrosis were common and polymorphonuclear leucocytes were present in appreciable numbers, whereas these were not characteristics of the cardiac lesion associated with acute and subacute glomerulonephritis. Within the time limits covered by these cases, progressive changes in the appearance of the lesions of the heart were not seen, as they so frequently were in the myocarditis associated with acute upper respiratory infections.

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*Frequently called the myocyte following Anitschkow's original interpretation, but generally recognized as a type of histiocyte. It plays a conspicuous role in the formation of the Aschoff nodule.

Though the differences between myocarditis of the two forms are clear cut, they do not nullify the role of the antecedent acute infection in the production of the heart lesion. Our knowledge of the lesion is limited to fatal cases in which there may be presumed to be a greater degree or even a different type of involvement than in nonfatal cases. The additional burden created by nephritis and its complications, if this premise is accepted, would be responsible for the fatal termination. Although recent acute infections were not mentioned in the histories of a significant number of these patients, many of the records were made under wartime field conditions and were not nearly as complete as those in other reported studies where the incidence of preliminary acute infections approaches 100 per cent (Whitehill and co-workers,[3] cited previously, reported 97.7 per cent). Two other mechanisms suggest themselves: the first, that the lesion in the heart musculature is the result of the acute nephritis; the second, that cardiac damage is due to the complementary effects of both the acute antecedent infection and the nephritis. The available information at this time does not permit a more definitive statement regarding the causative mechanism.

Nitrogenous retention was absent in only three (Cases 2, 14, and 16) of ten cases in which such blood chemistry studies were made; in an additional instance (Case 9) azotemia was only slight at the time cardiac manifestations had appeared. Such findings suggest, but further data are necessary to prove that uremia neither plays an essential role in the pathogenesis of the cardiac failure nor produces the heart injury by an indirect mechanism, such as the altered capillary permeability resulting from changes in blood and tissue electrolytes. They do tend to indicate the primary role of the heart lesion, although added factors may be the cardiotoxic effects attributed directly and indirectly to alterations of blood and tissue electrolytes in uremia. The morphologic character of the lesion suggests a capillary defect leading to increased extravasation of fluid, but the chronologic relation of such a defect to alterations in blood chemistry requires further study. The recognition of primary diffuse endothelial damage in acute glomerulonephritis is, of course, not a new concept.

The administration of sulfonamides to seven of these patients was not of etiological significance in producing the lesion under discussion. The character of the myocarditis was identical both in those who had received the drug and in those who had not. Furthermore, no case presented the lesions described by French[8] in sulfonamide hypersensitivity, namely, the vascular lesions and the perivascular infiltrates rich in acidophilic histiocytes and eosinophils.

Of fourteen hearts for which the figures were recorded, the weight exceeded 400 grams in ten, seven weighing 450 grams or more. Although hypertension is commonly regarded as the explanation for such enlargement, increased tension was present in only four cases (Cases 2, 6, 9, and 13). The elevation was moderate (200/90) in one, mild (158/100) in another, borderline (144/90) in another, and unstated in the fourth; the corresponding heart weights were 454, 450, 450, and 500 grams, respectively. The recorded blood tensions did not attain hypertensive levels in five other instances of cardiac enlargement (Cases 3, 4, 7, 8, and 10). Measurements of the blood pressure were not available for Case 5, nor were the cardiac weights reported in two additional cases without hypertension (Cases

11 and 16). Furthermore, it is questionable whether the degree of enlargement noted could be produced by an assumed moderate hypertension in the short course of the acute illness. For example, it is dubious whether a presumably normal heart could enlarge to 500 grams in ten days (as in Case 3) through muscular hypertrophy alone. The factor common to all the enlarged hearts, then, and the one not incompatible with the relatively short course of the illness is the serous myocarditis. There can be no doubt that such increases of interstitial fluid as are illustrated in accompanying photomicrographs would appreciably augment the weight of the heart.

These arguments must not be construed to deny the importance of hypertension in contributing to the cardiac enlargement observed. The possibility must be entertained that the relatively normal pressures recorded, though taken early during hospitalization, represented a certain degree of vasomotor collapse already present in acutely ill patients. It is generally accepted, though, that acute glomerulonephritis may occur and run its course without hypertension. Furthermore, cardiac enlargement in other forms of myocarditis without pre-existent hypertension has been attributed to the presence of the inflammatory exudate within the heart muscle.[9]

The therapeutic measures to be adopted are those commonly used in the treatment of other forms of cardiac decompensation. Failure to recognize this development, of which hypotension may be one manifestation, may result in the injudicious administration of fluids intravenously to combat "shock." Needless to say, such treatment may precipitate a fatal outcome.

SUMMARY

One hundred sixty cases of anatomically proved acute and subacute glomerulonephritis, exclusive of those subsequent to scarlet fever, typhus fever, or prolonged septicemia, were reviewed to ascertain the presence and the character of any concomitant myocarditis. Such a myocarditis was found to have occurred in sixteen patients; there were clear-cut clinical manifestations of myocardial failure in twelve, and in two others the clinical records suggested it. The symptoms were those common in other forms of heart disease; namely, cyanosis, arrhythmia, temperature-pulse disproportion, and hypotension. Electrocardiographic tracings were abnormal in three of the four cases in which they were available.

The increased heart weights, which were observed frequently, could be correlated better with the presence of myocarditis than with arterial hypertension, which had been noted in only four patients. The myocarditis had a distinctive character that differentiated it easily from that occurring as a result of sulfonamide hypersensitivity or after acute nasopharyngeal and tonsillar infections. Characteristically there was a widespread serous effusion into the interstitial tissues, increasing the space between the muscle fibers. The cellular elements were relatively sparse, consisting of lymphocytes, endothelial leucocytes, and Aschoff cells. The suggestion that myocardial damage is related to increased capillary permeability appears to coincide with the pathologic evidence. With regard to treatment, caution is recommended in the administration of intravenous fluids.

CLINICAL ABSTRACTS

CASE 1.—AIP Acc. 118909. A 26-year-old white man, who experienced progressive difficulty in breathing following a "cold" one week previously, was admitted to the hospital with cyanosis, dyspnea, "wet lungs," enlarged liver, and edema of the ankles. The heart sounds were poor; there was gallop rhythm. The pulse was rapid and thready. Despite morphine sulfate, aminophylline, and oxygen, there was progressive heart failure, and death occurred after one day.

CASE 2.—AIP Acc. 139746. A 37-year-old white man had noted swelling of the hands, feet, and ankles in the last five days of the course of a persistent upper respiratory infection of several weeks' duration. On admission there were facial edema, cardiac enlargement, and muffled heart sounds; blood pressure was 144/90. The roentgenogram showed pulmonary hilar congestion and a heart at the upper limits of normal size. There was moderate anemia, leucocytes numbered 7,000, and chemical composition of the blood was reported as normal. Although there was temporary improvement, dyspnea, tachycardia (140 per minute), gallop rhythm, and pulmonary edema developed suddenly on the fourth hospital day. Electrocardiograms showed changes compatible with myocardial damage. Treatment with morphine sulfate, aminophylline, digitalis, and oxygen was ineffectual, and death occurred on the following day.

CASE 3.—AIP Acc. 166013. A 40-year-old white man was admitted to the hospital with a two-day history of facial and ankle edema, lumbar pain, mild diarrhea, anorexia, and nausea. Urinalysis indicated acute glomerulonephritis; the blood showed considerable nitrogenous retention; the nonprotein nitrogen measured 162 mg. per cent, and the blood pressure was 118/70. The treatment was not specified. The blood nonprotein nitrogen rose to 195 mg. per cent. Tachycardia and pulmonary edema suddenly developed on the eighth day, and death followed rapidly.

CASE 4.—AIP Acc. 154657. A 25-year-old white man contracted a septic sore throat while hospitalized for a penetrating wound of the chest sustained one month previously. Sulfadiazine therapy was instituted. Three days later severe watery diarrhea and vomiting began suddenly, but were effectively combated with paregoric and belladonna. Although the temperature, which had been high, was now 99.4°F., there were physical signs and roentgenologic evidence of a pneumonic process at the base of one lung. A leucocyte count at this time showed a rise to 18,000 from a previous 7,000. Urinalyses were characteristic of acute glomerulonephritis; hemolytic streptococci were grown from a throat culture. The pneumonic process spread to involve both lungs; the temperature was 99.8°F.; the leucocyte count was 13,000; the blood pressure was 132/76. Except for the signs of the pulmonary process, the patient seemed improved. On the seventh day the temperature was 99°F. and the pharyngitis was less severe, but the pulse became weak and rapid and the respirations were labored. Mental disturbances appeared and the blood urea nitrogen measured 36 mg. per cent. The patient was transfused repeatedly. All of one lung except the apex became affected. Cyanosis appeared and persisted despite administration of oxygen. An electrocardiogram showed a prolonged P-R interval and marked sinus tachycardia. Death occurred quite suddenly on the twelfth day of the acute illness.

CASE 5.—AIP Acc. 146450. A 21-year-old white man was admitted to the hospital acutely ill with cough, anorexia, and vomiting of twelve days' duration. The patient was anemic; the white blood cells numbered 11,300. The urinalysis was typical of acute glomerulonephritis. The temperature was 104°F.; pulse rate, 90; and respirations, 24 per minute. There was marked dependent and pulmonary edema. Blood and plasma were given. Death occurred the day after admission.

CASE 6.—AIP Acc. 100802. A 28-year-old Negro man had a two-week history of pain in the lower back and shortness of breath. When admitted to the hospital he was febrile, with a temperature of 101.4°F., pulse rate of 92 per minute, and blood pressure of 204/90. The diagnoses were acute upper respiratory infection and hypertension. There was, however, mild pitting edema of the ankles and roentgenologic evidence of both central congestion of the lungs and an enlarged heart. Urinalysis indicated acute nephritis. Severe dyspnea developed the afternoon of admission; the temperature was 102.8°F., and the pulse rate was 88 per minute. The temperature rose to 105.2° F., and death occurred sixteen hours after admission.

CASE 7.—AIP Acc. 102628. A 20-year-old white man was admitted to the hospital with fever, sore throat, headache, and chills of two days' duration. The temperature was 100.2° F.; pulse rate, 104; and respirations, 24 per minute; white blood cell count was 24,000; blood pressure, 122/80. Physical examination disclosed marked edema and swelling of the throat with purulent exudate on the tonsils. (Two months previously the patient had been hospitalized for acute tonsillitis). Sulfathiazole was administered and frequent throat irrigations were given. On the fifth day, while the temperature was down and there was considerable improvement of the tonsillar infection; the urine showed the characteristic features of acute nephritis. The subsequent course of the illness was marked by oliguria, low-grade fever ranging from 98° to 100.6°F., and hypotension, the blood pressure measuring 90/40. Treatment consisted, in large part, of the administration of intravenous fluid. The blood nonprotein nitrogen rose from 45 mg. per cent on the sixth day to 120 mg. on the tenth hospital day. Precordial pain appeared on the eleventh day of hospitalization. The following day cyanosis, dyspnea, and weak and rapid pulse were noted. Heart sounds were poor and the patient still complained of precordial pain. Although oxygen was administered, death occurred on the thirteenth day.

CASE 8.—AIP Acc. 128718. A 21-year-old white man was hospitalized because of undue fatigability, cough, exertional dyspnea, and questionable edema of the face and extremities, dating from an acute attack of pharyngitis two weeks previously. Cyanosis, orthopnea, and anxiety were noticeable; the heart sounds were rapid and of poor quality. Signs of bronchopneumonia found on physical examination were confirmed roentgenologically. Urinalysis indicated an acute nephritis. The leucocyte count was 21,500. Despite the administration of sulfadiazine, penicillin, and oxygen, the cyanosis and dyspnea continued. Digitalization was started after a gallop rhythm developed. The patient expired on the third day with a temperature of 101°F., the highest fever attained.

CASE 9.—AIP Acc. 147313. A 31-year-old white man was hospitalized five days after the development of periorbital swelling, sore throat, shortness of breath, and dependent edema. There had been oliguria, and on admission the findings of dyspnea, pulmonary râles, and fullness of the upper abdomen suggested congestive heart failure. The heart sounds were normal; pulse rate, 70 per minute; and blood pressure, 130/78. The urine was typical of acute glomerulonephritis; the blood urea nitrogen was 21 mg. per cent. On the fifth hospital day pitting edema of the legs was noted despite bed rest and the use of digitalis. The blood pressure rose slowly to a maximum of 158/100 on the twelfth day. On the thirteenth hospital day the patient died suddenly after the onset of acute "cardiac pain."

CASE 10.—AIP Acc. 145515. A 38-year-old white man was admitted to the hospital a week after extreme weakness and edema of the face and lower extremities had appeared. He was afebrile, and the blood pressure was 140/80. The urinary findings were characteristic of acute glomerulonephritis. Medication consisted of theophylline daily. The patient remained afebrile; one week after admission, cyanosis, short, shallow respiration, pulmonary edema, ascites, and dependent edema were noted. The heart sounds were rapid and distant and the roentgenogram showed cardiac enlargement and pulmonary congestion. Death occurred on the ninth day despite the administration of aminophylline and digitalis.

CASE 11.—AIP Acc. 108334. A 49-year-old white man was dyspneic, cyanotic, cold, perspiring, and confused when admitted to the hospital. He had been ill for one week and bedridden for three days with pleural pain and fever. The temperature was 98°F. and there were physical signs of pneumonia in the right lung. Heart sounds were faint; the pulse was weak and rapid (146 per minute); the blood pressure was 90/60. Sulfadiazine was administered and oxygen given. Hemolytic streptococci were grown from the sputum. By the fourth day there was definite improvement. The pulse and heart action were better, cyanosis was no longer present, temperature was 99°F., and pulse was 100 per minute. Sulfadiazine was discontinued. Oliguria was noted on the ninth hospital day; also mental confusion and incontinence. The blood pressure was still low. The nonprotein nitrogen reached 130 mg. for each 100 c.c. of blood on the twelfth day and 214 mg. on the sixteenth day despite efforts to increase renal function. Urinalyses were characteristic of acute glomerulonephritis. Mental confusion and increasing weakness dominated the remainder of the

clinical course during which Cheyne-Stokes respirations and weak heart action were noted. Death occurred on the nineteenth day in the hospital.

CASE 12.—AIP Acc. 158943. A 28-year-old white man was admitted to the hospital with headache, backache, nausea, vomiting, and periorbital edema. He had scarcely recovered from an attack of acute nasopharyngitis which had originated two weeks earlier. The urinary findings indicated acute glomerulonephritis. The blood pressure measured 150/90. Oliguria, gross hematuria, edema, and increasing azotemia were associated with marked mental aberration. Treatment had included several transfusions of blood and plasma. Terminally, the nonprotein blood nitrogen measured 120 mg. per cent, and the patient died on the twentieth day in the hospital.

CASE 13.—AIP Acc. 148005. A 42-year-old white man had had his left leg amputated three weeks following the shattering of his ankle by a shell fragment. During the next month there was low-grade intermittent fever and mild diarrhea improved by a two and one-half week course of sulfadiazine. One and one-half months following the amputation, pneumonia developed rather suddenly. Though the temperature responded promptly to penicillin, dyspnea, cyanosis, dependent edema, and hydrothorax developed. The heart rate was raised and at times irregular. The urine which had been previously normal now contained large amounts of albumin and numerous red and white cells. Digitalis proved of no avail and the patient died four weeks after the onset of the pneumonia. Hypertension of unstated degree had been noted during the last month of illness.

CASE 14.—AIP Acc. 102428. A 20-year-old white man was admitted to the hospital with a five-day history of nasopharyngitis, a fever of 101°F., cough, constant "epigastric pain," and swelling of the hands and feet. Three weeks previously he had had an acute pyogenic infection of an epidermophytosis of the foot with fever of 102°F., lymphangitis, and swollen lymph nodes. This infection had been effectively treated with hot applications and with sulfonamides. The urinary picture indicated acute glomerulonephritis. Nonprotein nitrogen measured 35 mg. for each 100 c.c. of blood. Temperature ranged from 98° to 101°F. and pulse rate, from 100 to 120 per minute. Purpuric skin lesions occurred in successive crops. Epistaxis was observed on the tenth day; abdominal pain became more severe. On the eleventh day there was apathy and mental aberration. Death followed the sudden development of pulmonary edema on the twelfth day. White blood cell counts ranged between 9,600 and 14,600; differential counts and cell types were normal. Platelet counts, measurements of bleeding and clotting times, and prothrombin determinations failed to produce evidence to account for the purpuric manifestations.

CASE 15.—AIP Acc. 103282. A 30-year-old white man was hospitalized because of urinary evidence of acute nephritis. For one month previously there had been intermittent bouts of diarrhea, anorexia, nausea, and vomiting, treated with variable success with bismuth preparations, paragoric, and sulfaguanidine. On admission, the temperature was 90° F.; pulse, 58; blood pressure, 100/64; the blood urea nitrogen was elevated; and the leucocytes numbered 9,900. There was oliguria which progressed to anuria after the third day. Signs of mild pulmonary edema were found on the sixth day; an electrocardiogram was normal; the sedimentation rate was greatly accelerated. Treatment consisted of frequent intravenous instillations of fluids to induce diuresis. Death occurred on the eighth day after admission to the hospital.

CASE 16.—AIP Acc. 151123. A 32-year-old white man was admitted to the hospital with fever, sore throat, and cough of ten days' duration. The temperature was 100.6°F.; pulse rate, 80; respirations, 18 per minute; blood pressure, 138 80. Leucocytes numbered 4,300. Urinalyses showed albuminuria, hematuria, and casts. The course was persistently febrile with temperatures ranging from 101° to 104° Fahrenheit. Blood cultures were repeatedly sterile. Facial edema developed on the seventeenth day; cardiac enlargement was noted radiologically on the nineteenth day. Supportive treatment had included frequent transfusions of blood and plasma. Auricular fibrillation developed on the fortieth day and despite digitalization, death occurred three days later. Blood nitrogen determinations were repeatedly within normal limits, as were the blood pressures taken many times.

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ANEURYSM OF THE CORONARY ARTERIES

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In 1929, Packard and Wechsler[1] observed a case of aneurysm of the left coronary artery with rupture. In reporting this they made an extensive search of the literature and found the earliest report of aneurysm of the coronary vessels to be that of Bougon[2] in 1812. In their review they eliminated all cases of periarteritis nodosa and apparently also eliminated those of "diffuse aneurysm," or generally dilated vessels, limiting the cases they considered bona fide to localized enlargements and thereby including only saccular and fusiform aneurysms. They considered that most cases they reviewed could be classified as either mycotic-embolic or arteriosclerotic. Their reason for calling the latter group arteriosclerotic in type was merely the fact that all cases showed some atherosclerosis and there was no definite evidence to indicate what the exact origin was. Two bona fide cases of localized coronary aneurysm reported prior to 1929[3,4] were not included in their review. The case of Bristowe,[5] which they eliminated as being periarteritis nodosa, does not include sufficient data to verify this diagnosis clinically; microscopic description is lacking, and the author clearly indicates that there was no involvement in the other arteries of the body. However, this case will not be added to the present review.

Since their report, there has been an average of one report of coronary aneurysm annually, and the various authors have used the term "aneurysm" in its broadest sense, including all types of dilatations, as well as dissecting aneurysm, in enumerating the cases to date.

Recently, at the Mallory Institute of Pathology, an 84-year-old man was autopsied who had a coronary aneurysm which in size is unique in the annals of medical literature. It is the only case of this type which has been recorded at this institution, where there are 19,403 autopsies on file (Jan. 1, 1947). This case is reported herewith, and in order to clarify the present status of aneurysm of the coronary arteries a review of the literature since 1929 with tabulation of essential data has been made (Tables I and II).

Of the cases commonly mentioned and enumerated in recent reviews, two will be eliminated from further discussion. Schuster's report[6] was of an aneurysm of the sinus of Valsalva, involving secondarily the orifice of the left coronary artery, and no other portion of either coronary artery. Westerlund's case[7] had only an aneurysm of the left ventricular wall, which followed coronary occlusion

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Table I. Clinical and Pathologic Findings in Reported Cases. The Classification is Based on Structure

	AUTHOR	AGE	SEX	PREVIOUS HISTORY	SYMPTOMS AND TYPE OF DEATH	SITE	SIZE	CORONARIES	OTHER PATHOLOGIC CHANGES
					Localized Aneurysms				
1	Abbott (1908)[3]	60	F	No cardiac symptoms (No other clinical data given)		Right coronary just distal to origin	"Crab-apple" 2.5 cm. above epicardium	Thick-walled, wide tortuous channels	Left coronary originated from pulmonary artery, and there were anastomoses with right coronary artery; flow was thought to be toward pulmonary artery
2	Trevor (1912)[4]	11	F	Onset of chills and fever 22 days before death Harsh tricuspid to-and-fro murmur 5 days before death. Blood culture: positive *Streptococcus viridians*	Died from sepsis	Right coronary, termination of a dilated portion	"Plum"	Right coronary dilated to 1 cm.	Aneurysm ruptured into right ventricle at inner side of anterior papillary muscle with organized thrombus at the site
3	Abbott and Chase (1929)[14]	34	M	Athlete, rejected for military service in World War I for "Athlete's Heart"; 1 year prior had had repeated colds and fainting episodes	4 weeks before death had chills and fever with emboli to hands and feet, precordial pain; died suddenly	Left circumflex	"Walnut"	Thrombosis in circumflex branch of left coronary distal to mycotic aneurysm	Aneurysm ruptured into left auricle; fibrohemorrhagic pericarditis; bicuspid aortic valve with vegetations which showed *Streptococci*; "false aneurysm" at base of heart, "hen's egg" in size
4	Cox and Christie (1930)[15]	65	M	Hypertension several years; dyspnea and edema 10 months, without response to digitalis and diuretics after first 2 months	Moribund several days before death, expired quietly	Right coronary, several cm. distal to origin	2.5 × 4.0 cm. (fusiform)	Markedly sclerotic	Right coronary anomalous; thrombosis left anterior descending branch with healed infarct; marked atherosclerosis of aorta, saccular aneurysm 11 cm. diameter

5	Vogelsang (1930)[16]	38	M	Compression injury to chest 3 months before death; pain on inspiration and pressure and prickling sensations in heart region thereafter	3 days before death began coughing up bright red sputum; died suddenly	Left coronary, anterior descending branch	6.0 × 5.5 × 4.5 cm.	Thickening of intima with obliteration of lumen, perivascular round cell infiltration, thrombosis distal to aneurysm	Gummata in right ventricular wall; gummatous myocarditis, periarteritis, and endarteritis with vascular fibrosis and plasma cell infiltration in connective tissue
6	Domenishini (1934)[17]	77	M	No clinical	data given	Left coronary	"Nut"	Moderately sclerotic	Thrombosis in aneurysm and in vessel distally
7	Snyder and Hunter (1934)[18]			Clinical data	unknown	Left coronary, 5.0 mm. from origin	3.5 × 2.0 × 1.0 cm.	Plasma cell and lymphocyte infiltration of walls with fragmentation of elastica	Syphilitic mesoaortitis with saccular aneurysm of ascending aorta, aneurysm of sinus of Valsalva lying next to coronary aneurysm
8	Eliasoph (1935)[19]	58	M	10 years of increasing dyspnea, orthopnea, and headaches; nocturnal dyspnea for 5 years; ECG showed myocardial damage	Cardiac decompensation with no response to digitalis and diuretics; gradually lost ground and expired quietly	Left coronary, 1.0 cm. distal to origin	7.0 mm.	Marked atherosclerosis	Many small coronary occlusions; *large aneurysmal dilatation of left* ventricle with degeneration of septum
9	Seydel (1935)[20]			No clinical	data given	Left coronary, anterior descending branch	"Pea" ("Umgefahr Erbsengrosse")	Marked atherosclerosis	Scarring and fibrosis of myocardium; syphilitic aortitis
10	Rae (1937)[21]	2-9/12	M	Pale and listless for 1 month; joint tenderness, fever, lymphadenopathy; weak and had "blue spells" for 9-10 months	Fever to 101° F. that subsided, but leucocytosis with many immature forms persisted; sudden death	Left coronary Right coronary	1.5 cm. diameter 1.0 × 2.0 cm.	Exudative necrotizing reaction in vascular walls	Fibrinous pericarditis, thrombosis of aneurysm on right coronary, and rheumatic carditis
11	Chiari (1938)[10]	34	M	5 weeks' history of pain in chest and dyspnea with gradually increasing palpitation	Died of congestive failure	Right coronary, 5.0 cm. from origin	10.0 × 7.0 cm. with constriction in midportion	Slight atherosclerosis	Pulmonary artery compressed by aneurysm; right auricle and ventricle dilated; funnel-shaped origin of right coronary; no elastica in wall of aneurysm

Table I. Clinical and Pathologic Findings in Reported Cases. The Classification Is Based on Structure—Cont'd

	AUTHOR	AGE	SEX	PREVIOUS HISTORY	SYMPTOMS AND TYPE OF DEATH	SITE	SIZE	CORONARIES	OTHER PATHOLOGIC CHANGES
12	Manohar (1938)[22]	Adult	M	Penile lesion many years previously; aneurysm of abdominal aorta diagnosed by x-ray; pain in back and legs for 3 months	Rumbling systolic sound in 3rd left intercostal space; collapsed and died suddenly	Left coronary, just distal to origin	1.5 × 1.0 cm.	Gummatous changes in wall of aneurysm and general thickening of intima	Rupture of aneurysm of celiac artery; hepar lobatum; positive Kahn and Wassermann tests on post-mortem serum
13	DeNavasquez (1939)[23]			No clinical data given. Case is listed incidentally in a review of 20 hearts from proven cases of *Streptococcus viridans* subacute bacterial endocarditis		Left coronary, descending branch, halfway to apex	1.0 × 1.0 cm. (mycotic)	Occlusion of vessel proximal to aneurysm	Myocardial infarction of left ventricular wall
14	Chipps (1942)[24]	45	M	Rheumatic endocarditis 20 years previously; chills and fever 6 months; blood culture positive for *Streptococcus viridans*	Severe constricting pain in chest followed by gradual improvement for 10 days; then sudden death	Left coronary, anterior descending branch, 2.0 cm. from origin	1.9 × 1.6 cm. (mycotic)	Vessel occluded distal to aneurysm	Embolus to left pulmonary artery; heart weight: 660 grams; bacterial endocarditis on mitral valve; aortic stenosis
15	Rigdon and Vandergriff (1943)[11]	33	M	Sudden onset substernal pain 15 days before death; ECG showed evidence of left coronary occlusion with infarction	Developed acute respiratory distress with pulmonary edema and died 4 hours later	Left coronary Right coronary	2.0 × 1.5 cm. 1.0 × 2.0 cm. 1.0 × 2.0 cm. 1.0 × 2.0 cm.	Loss of elastica and thinning of muscularis in wall of aneurysm	Thrombosis of anterior descending branch, left coronary, just distal to aneurysm
16	Marano and associates (1945)[25]	43	F	Past history of rheumatic fever; negative Kahn and Wassermann; ECG evidence of myocardial damage	Gradual onset of dyspnea and palpitation over period of years; died in congestive failure	Right coronary	1.0 × 0.7 cm.	Slight athero-sclerosis	Aneurysm ruptured; syphilitic mesoaortitis; plasma cell and lymphocyte infiltration of media and adventitia with loss of elastica and hyalinization

					Diffuse Aneurysms				
1	Halpert (1930)[26]	54	M	Pains in knee joints, no cardiac complaints	Died from carcinoma of stomach with metastases to liver	Right coronary	1.5 × 2.0 × 20 cm.	Slight atherosclerosis	Arteriovenous communication at termination of enlarged vessel
2	Nagoya and Takahashi (1932)[27]	72	M	Puny in childhood, but no complaints in later life until age 61 years when precordial pain, palpitation, and dizziness followed by dyspnea and cyanosis; joint pains at ages 63 and 68 years	Sudden precordial pain with dyspnea; edema and coma followed; died 1 day later	Left coronary, circumflex branch	1.0 to 1.8 × 21.5 cm.	Marked atherosclerosis	1.0 mm. opening into coronary sinus at termination of dilated vessel; mural thrombus in coronary sinus; recent infarct of left ventricle
3	Lowenheim (1932)[28]	62	F	Cardiac symptoms for 2 years, blood pressure up to 260/100	Gradually progressing congestive failure	Right coronary	2.0 cm. diameter for length of vessel	Vascular walls thickened	Heart weight, 835 grams; arteriovenous communication at termination of dilated vessel, veins also dilated
4	Kockel (1934)[29]	38	M	10-year history of precordial discomfort	Found dead; no information on immediate symptoms	Right coronary	0.6 to 1.2 cm. diameter for length of of vessel	Slight atherosclerosis	Left coronary originated from pulmonary artery, right coronary supplied entire heart with arterial blood
5	Harris (1937)[30]	43	M	No known cardiac symptoms	Died from hemorrhage into brain tumor	Right coronary	0.7 × 13 cm.	Slight atherosclerosis	Aneurysmal vessel is anomalous branch of right coronary which terminated directly into chamber of right auricle; remainder of right coronary not enlarged and had normal distribution
					Miscellaneous Types (Dissecting)				
	Pretty (1931)[8]	42	F	30 hours before death, onset of nausea and vomiting with pain in the chest	Was fairly comfortable and did not appear terminal, when death occurred suddenly	Right coronary	—	Atherosclerosis of all coronary vessels, with dissecting aneurysm on right	—

TABLE II. ETIOLOGIC CLASSIFICATION OF LOCALIZED ANEURYSMS

	ORIGINAL CLASSIFICATION			SUGGESTED REVISION							
	MYCOTIC-EMBOLIC	ARTERIO-SCLEROTIC	OTHERS OR UN-CLASSI-FIED	MYCOTIC-EMBOLIC	ARTERIO-SCLEROTIC	CON-GENITAL	SYPHI-LITIC	PURE MYCOTIC	RHEU-MATIC	PROBABLY PERI-ARTERITIS NODOSA	UNCLAS-SIFIED
Bougon	x			x							
Merat			x								x
Hedlund			x								x
Peste		x				x					
Peacock		x				x					
Heuse			x							x	
Finnell			x								x
Markoe			x								x
Wood		x				x					
Ogle	x			x							
Buchner		x				x					
Gee			x			x					
Crisp		x				x					
Malet and Evans			x			x					
Eppinger	x			x							
Clarke			x							x	
Capps		x				x					
Capps		x					x				
Griffith	x			x							
Griffith	x			x							
Toller	x ?			x ?							
Ruge			x					x			
Winkler		x			x						
Henke	x			x							
Somner		x				x					
Martland		x					x				
Fraenkel			x			x					
Lublin	x			x							
Windholz		x			x						
Packard		x			x						

Reported Subsequent to 1929 or Not Included in Above

Abbott			x					
Trevor	x							
Abbott and Chase	x							
Cox and Christie			x					
Vogelsang				x				
Domenishini		x						
Snyder and Hunter				x				
Eliasoph		x						
Seydel		x						
Rae						x		
Chiari			x					
Manohar				x				
DeNavasquez	x							
Chipps	x							
Rigdon and Vandergriff			x					
Marano, Baila, and Cardeza				x				
Scott			x					
	12	6	15	6	1	1	2	4

Classification of cases reported prior to 1929 is from data in table published by Packard and Wechsler.[1]

that had been preceded by carbon monoxide poisoning, with no aneurysm of the arteries.

In the accompanying Table I the reports are divided into two main groups according to structure: (1) Localized aneurysms, including saccular, fusiform, mycotic, and so forth, and (2) diffuse aneurysms, including all in which a vessel was generally increased in diameter.

Only one case cannot be satisfactorily classified in either of these groups. It is the case of dissecting aneurysm reported by Pretty[8] in which no mention is made of the size of the vessel. There is some question as to whether this case should be included; however, it is listed and data given to permit the reader to decide whether he chooses to count it.

Analysis of the thirty cases listed by Packard and Wechsler (including the one they presented) showed several interesting features: there was no particular age distribution; the condition was present much more commonly in men; about one-half of the cases had rupture of the aneurysm; and only three cases gave any history of trauma that might have been contributory and this was discounted. Only three patients showed an associated syphilitic mesoaortitis and seven gave a definite history of rheumatic fever, while one other had had rheumatic pains. Other medical complications were scarletinal nephritis, generalized arteriosclerosis, and "cardiac disease." They were unable to show any pathognomonic clinical findings on which to establish the diagnosis, and they observed that sudden death caused by rupture of the aneurysm (occurring fourteen times) was the most common cause of death, while gradual heart failure was a cause in others. They made the observation that aneurysms usually occurred in the first part of the vessel concerned, or at the bifurcation of vessels, and that the condition occurred singly much more frequently and involved the left coronary more often than the right.

Four possibilities as to etiology were discussed with the pathogenesis for these types discussed in some detail: mycotic-embolic, arteriosclerotic, pure mycotic, and traumatic. All the cases were classified in one of the first three groups or were unclassified. One was considered pure mycotic; seven were definitely mycotic-embolic, with another considered to be probably in this group; and twelve were thought to be arteriosclerotic. Of the remaining nine, two were considered to be probably periarteritis nodosa and seven were not classified, four of which had insufficient data for any attempt at classification. The remaining three were similar in many features to the arteriosclerotic, but occurred at the ages of 5, 7, and 20 years and showed no atherosclerosis.

The possibility of congenital aneurysm or of an aneurysm developing on the basis of congenital defects in structure of the vascular wall was not considered. Since their paper was written, Forbus[9] has advanced the idea that aneurysms of the cerebral arteries are probably usually on this basis. He demonstrated defects in coronary vessels as well as in cerebral vessels, although the former were much less common. Other authors[10,11] expressed the opinion that many coronary aneurysms are of similar origin. The case of Rigdon and Vandergriff[11] had multiple aneurysms, all located at points of bifurcation; as pointed out by Forbus,[9] this is the locality where fusion of the muscularis in embryonic life is

apt to be incomplete and it is here that the elastic lamina is weakest. In support of the concept that more of the cases of doubtful origin are due to some congenital defect rather than to an arteriosclerotic process is the fact that they have been found in cases with minimal atherosclerosis and have been seen as early in life as 5 years and as late as 84 years, with the youngest showing no appreciable atherosclerosis and the oldest showing minimal involvement. Another factor is the occasional presence of other associated congenital anomalies in the heart. Possibly it would be wiser to leave this large group as unclassified until further evidence can be obtained to indicate more definitely what the etiology is. However, it does not seem unreasonable to consider them as congenital unless definite evidence indicates otherwise. Doing so would leave unclassified only those cases in which information is too meager to eliminate them from other possible groups.

Against the concept that these aneurysms are of arteriosclerotic origin is the fact that they are often seen in vessels with minimal atherosclerosis; that there are not uniformly atheromas at the sites of the aneurysms; that the aneurysmal walls often have well-localized, circumscribed, calcareous deposits within them, and these do not appear to be causing any disruption of the continuity of the vessel walls; and that some previously classified as arteriosclerotic were as large as 6.0 cm. in diameter, which seems a rather excessive degree of dilatation for a sclerotic vessel without the formation of a "false aneurysm" by rupturing into the surrounding tissue. Also one would expect to find some of these "false aneurysms," as well as the incidence of rupture, if the dilatation were due to destruction of the vascular wall by a degenerative process such as atherosclerosis. Furthermore, the average age of the patients classified by Packard and Wechsler as arteriosclerotic, which was 57 years, would be expected to be associated with a high incidence of atherosclerosis no matter what the etiology of the aneurysm. Most cases of this group on which microscopic studies have been made showed loss or diminution of the elastic lamina and replacement of the muscular fibers in the media by collagen, but very little mention is made of the presence of atheromas in the larger aneurysms.

Another etiological factor which received little consideration by Packard and Wechsler was syphilis, although three of the cases, including their own, showed associated syphilitic aortitis, and one of these showed involvement of the aortic valve. They considered syphilis as a possible factor in these cases but discounted it in favor of arteriosclerosis. One of these, reported by Martland[12] and considered to be syphilitic by him, was 6.0 cm. in diameter and was associated with an aortic aneurysm, as well as a syphilitic mesoaortitis, while the coronaries were not particularly atheromatous. Since their paper was written, Moritz[13] has demonstrated definite syphilitic endarteritis of coronary arteries as far as 12 mm. from the aorta.

It is not intended in this discussion to imply that atherosclerosis is not to be considered an etiological factor in the formation of aneurysms of medium-sized arteries. However, it does seem worth while to raise the question of how large a true aneurysm can be attributed to this condition and whether definite evidence in regard to degree of atherosclerosis should not be required before considering it to be of etiological significance. In view of this discussion, the data

on the cases reviewed by Packard and Wechsler have been examined and a reclassification suggested as in the accompanying table (Table II), considering as arteriosclerotic only those cases which are associated with a high degree of atherosclerosis at the site of the aneurysm.

Combining the data from previous reports with that of the case herewith reported, certain observations seem worthy of comment. In all there have been forty-six cases of localized aneurysms of the coronary arteries reported, and the present case brings the total to forty-seven.

SURVEY OF DATA

Type.—The most common type appears to be the congenital, with fifteen being so classified. The next in frequency are the mycotic-embolic, with eleven definite and one probable, for a total of twelve. There have been six arteriosclerotic and six with evidence to indicate syphilis as the most significant etiological factor. One was the result of acute rheumatic fever and one was purely mycotic. Two were probably periarteritis nodosa, but could not be eliminated from the series because the reports contained no description of the histology, and there was no other information on which to make this diagnosis. Four cases must remain unclassified because of insufficient data.

Since 1929, there have been reported five diffuse aneurysms of coronary vessels, all of which seem to have been of congenital origin. Three of these were associated with arteriovenous communications and one showed a connection directly into the right auricle, while the other was a right coronary artery that furnished the entire arterial blood supply to the heart, because the left originated from the pulmonary artery.

One dissecting aneurysm of the right coronary artery has been reported.

Location.—Of the forty-seven cases with localized aneurysm, the location in three is not specified. In the remaining forty-four, twenty-seven involved the left coronary only, eleven involved the right only, and six showed involvement of both. Thirty-six were single and eight were multiple, the remaining three being presumably single.

In the group with diffuse aneurysm, the right coronary artery was affected in four, while the left coronary was affected in only one.

The one case of dissecting aneurysm was of the right coronary artery.

Age.—(Based on the cases in which age was given by the author.) In the congenital group, fourteen patients ranged in age from 5 to 84 years, and the average was 47.1 years. Nine cases in the mycotic-embolic group occurred between the ages of 11 and 45 years, with an average of 29.7 years. Five ateriosclerotic aneurysms occurred between the ages of 58 and 77, the average being 65 years. Four patients in whom syphilis was a factor were between the ages of 32 and 43, with the average being 38 years. In the remaining cases in these groups, the age of the patient was not stated.

Sex.—In the fifteen congenital cases, fourteen patients were men and one was a woman. In the mycotic-embolic group, where the sex was known, six were men and four were women. Of the arteriosclerotic group there were four men and one woman, while in the syphilitic group there were three men and two women. Of the others, there were four men, three women, and in five cases the sex of the patient is not known. While these figures are not statistically significant, it is of interest to note that among the infectious types the ratio was three men to two women, whereas in the others the men were in great preponderance.

Cause of Death.—The commonest cause of death in the cases of localized aneurysm reported prior to 1929 was rupture of the aneurysm, but this complication developed only twice since then. The commonest cause of death since 1929 has been coronary thrombosis, which occurred nine times. In all but one of these,[15] either the aneurysm or the vessel distal to it was thrombosed. Chronic congestive failure occurred in three cases, including the case of Cox and Christie, which had coronary occlusion. Death was due to rupture of an abdominal aneurysm in one[22] and to complications from carcinoma of the prostate in one (present report). In two[18,14] the complete protocols were not available and the findings in the hearts did not adequately explain the deaths.

Clinical Features.—There were no clinical findings which would suggest an aneurysm of the coronary arteries. The symptoms, when there were any present, were those associated with coronary occlusion, with chronic heart disease, or sudden death took place.

CASE REPORT

W. L. (Hospital No. 1,213,451), an 84-year-old white man, was admitted to the Boston City Hospital on Aug. 5, 1946, with acute urinary retention. His past history revealed no illnesses of any consequence and he denied symptoms referable to other systems. Physical examination revealed nothing significant except a distended bladder and an enlarged, nodular, indurated prostate. The lungs were slightly emphysematous and the heart was not enlarged to percussion. The heart sounds were of good quality, without murmurs. The temperature was 100° F.; pulse, 95; respirations, 22; and the blood pressure, 120/70. Serologic test for syphilis (Hinton) was negative on Aug. 5, 1946. A clinical diagnosis of carcinoma of the prostate was made.

On preoperative chest x-ray study he was found to have a large, globular shadow on the right border of the heart (Fig. 1). At fluoroscopy this was seen to pulsate and the esophagus was displaced posteriorly and to the left (Fig. 2). A diagnosis of probable aneurysm of the right auricle was made. An electrocardiogram showed premature auricular beats and a shifting pacemaker, but was otherwise within normal limits (Fig. 3). X-ray films of kidney, ureters, and bladder, as well as an intravenous pyelogram, were normal except for an enlarged bladder.

Since he was asymptomatic from the cardiac viewpoint, it was deemed safe to proceed with surgery, and on Aug. 14, 1946, a bilateral orchidectomy was performed under local anesthetic. He had practically no reaction and on Aug. 22, 1946, a transurethral prostatic resection was done under spinal anesthesia.

Preoperatively his blood nonprotein nitrogen had been 37 mg. per 100 c.c., and immediately postoperatively it was 31. He responded well for eight days following the operation. At that

Fig. 1.—(W. L. No. 1,213,451). X-ray of chest taken at seven feet, showing large, globular mass extending to right of heart.

time he became somewhat stuporous and his blood nonprotein nitrogen was found to be 101 mg. per cent. During the following ten days this fluctuated, but gradually rose to 170; the carbon dioxide combining power dropped to 11 volumes per cent and he died in coma on Sept. 9, 1947.

At no time did he have any complaints referable to the heart or chest.

Clinical Diagnoses.—Carcinoma of prostate. Terminal uremia. Bronchopneumonia. Auricular aneurysm.

Autopsy.—(A46-473.) Performed Sept. 9, 1946, eight hours post mortem. The anatomic diagnoses were: (1) adenocarcinoma of the prostate with local invasion; (2) chronic cystitis with hydroureters; (3) severe bilateral acute pyelonephritis; (4) arteriosclerotic heart disease, mild; (5) anomalous coronary circulation with multiple aneurysms; (6) bronchopneumonia, both lower lobes; (7) fibrous pleural adhesions, left; (8) diverticulosis of colon and sigmoid; and (9) hepatitis, early, acute suppurative with focal necrosis.

On opening the chest cavity the heart was seen to be enlarged to the right. The enlargement consisted of a firm, globular mass measuring 10 by 8.0 by 8.0 cm. (Fig. 4), which on section was found to contain a laminated blood clot with fresh blood at the center of the laminations (Fig. 5). There were multiple small, saccular areas on the surface of the heart at the base of the aorta and pulmonary artery. There was another mass, 3.0 by 2.0 by 1.8 cm., on the anterior surface of the larger one. The myocardium was not remarkable except for a few scattered strands of fibrosis. The epicardium and the endocardium were not remarkable. The valves were thin and pliable. Heart weight: 780 grams. The wall of the right ventricle was 0.2 to 0.3 cm. in thickness; that of the left ventricle, 0.8 to 1.5 centimeters. Circumferences of valve rings were: tricuspid, 13.0 cm.; pulmonary, 8.5 cm.; mitral, 12.0 cm.; and aortic, 8.0 centimeters.

Fig. 2.—(W. L. No. 1,213,451). X-ray of chest with barium in esophagus, showing displacement to the left.

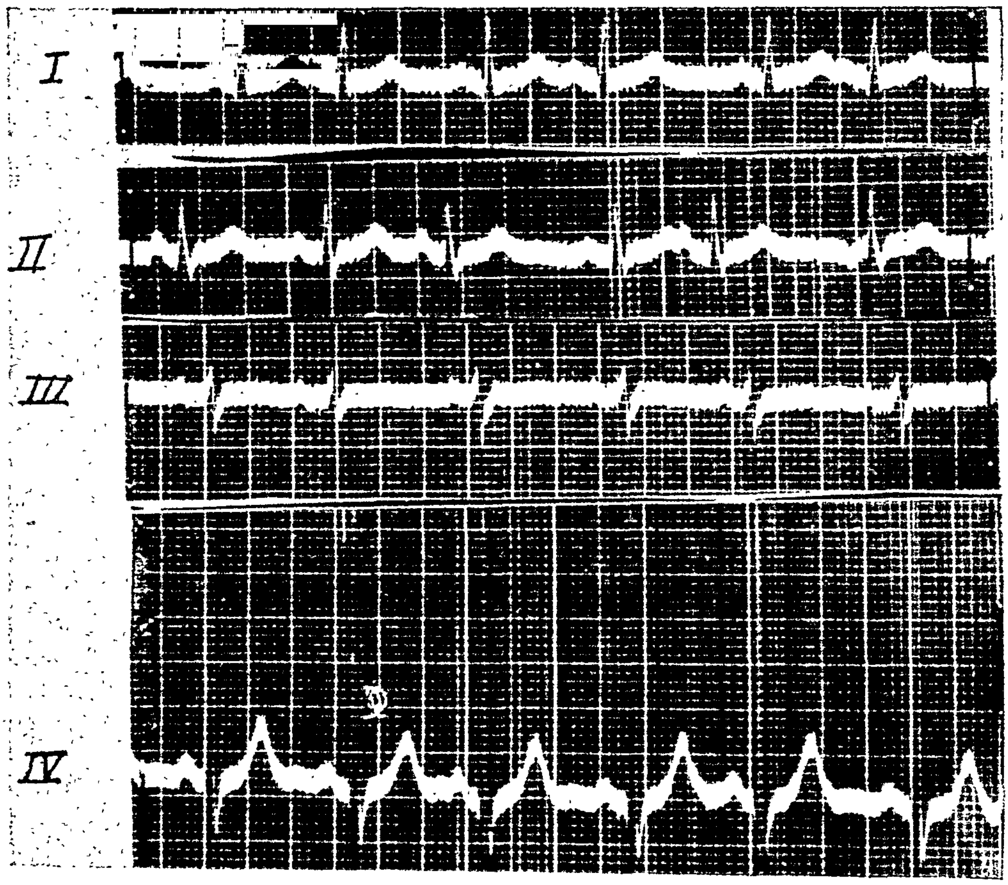

Fig. 3.—(W. L. No. 1,213,451). Electrocardiograph showing premature auricular beats and shifting pacemaker.

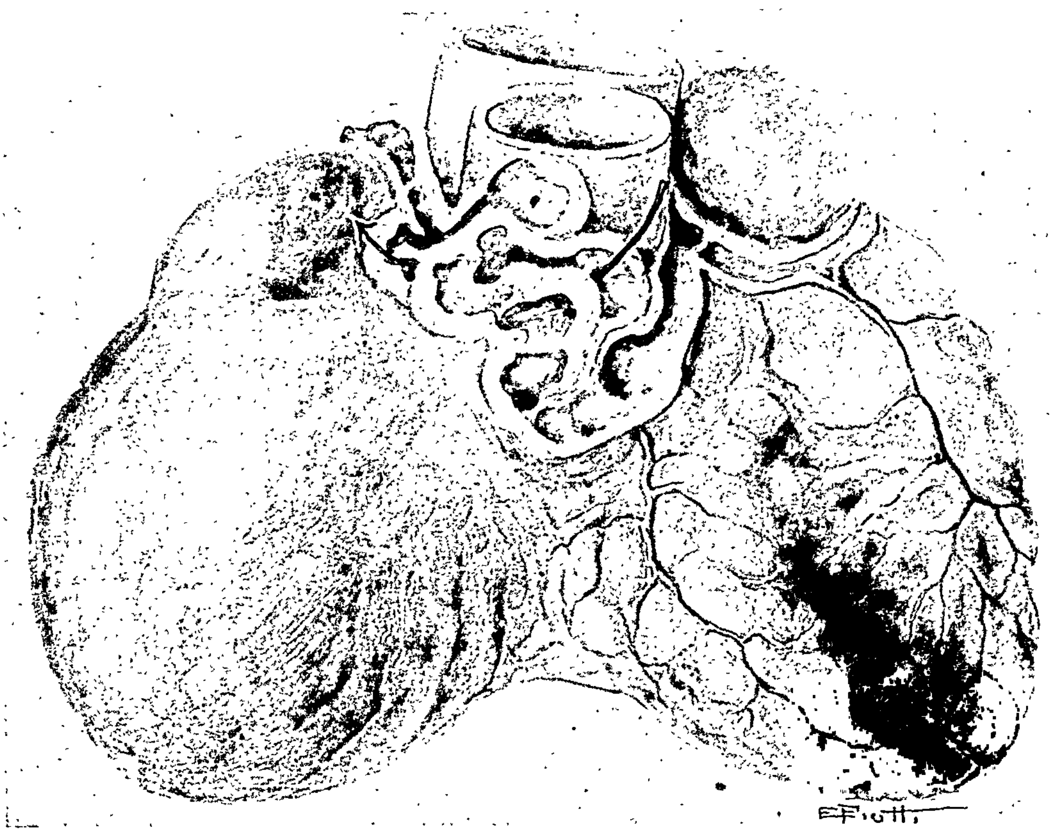

Fig. 4.—(W. L. No. 1,213,451, A46-473). Drawing of heart showing anterior view with large aneurysm to left. Anomalous vessel *connecting* anterior descending branch of left coronary to accessory right coronary is shown in detail. (Compare with Fig. 6.)

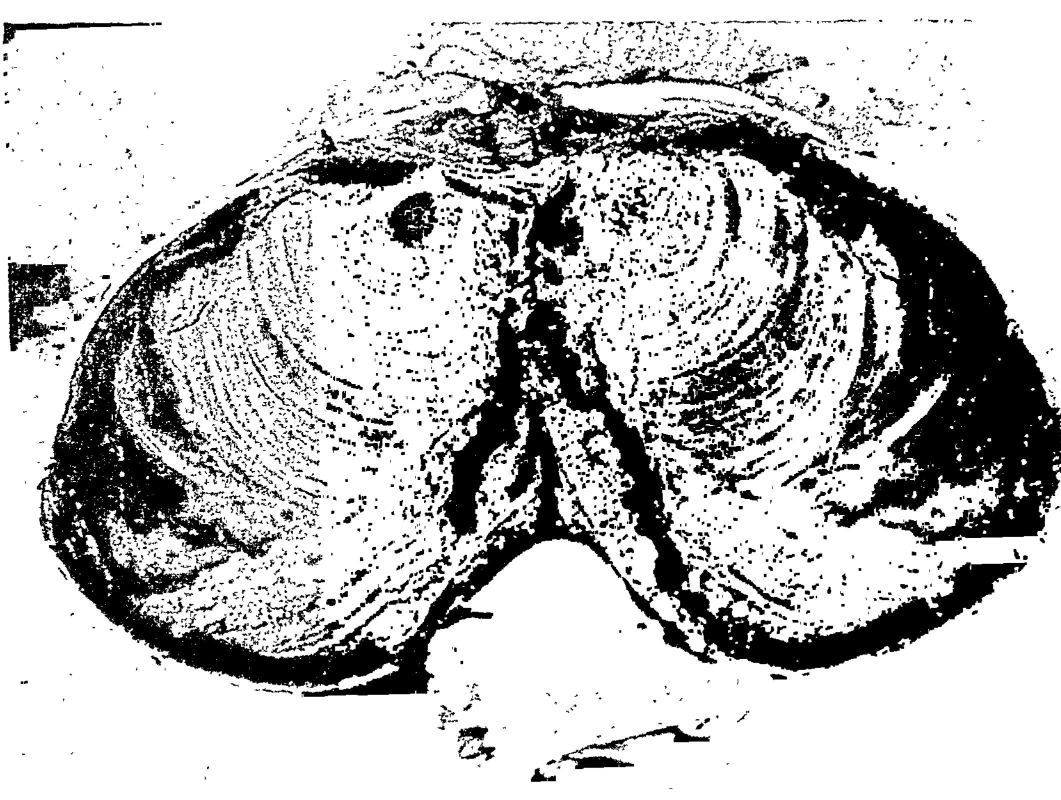

Fig. 5.—(W. L. No. 1,213,451, A46-473). Section through large aneurysm showing concentrically laminated thrombus with fresh blood at the *center of laminations.*

In dissecting the coronary arteries (Fig. 6) there were found to be two ostia in the right sinus of Valsalva and one in the left. These were not remarkable in appearance. From the right, one entered a vessel that followed the usual course of the right coronary artery, and was not remarkable except for a few atheromatous plaques. The other entered a vessel which proceeded 3.1 cm. anteriorly into the aneurysm measuring 10 by 8.0 by 8.0 cm., from which it emerged and, following a tortuous course, entered the aneurysm which measured 3.0 cm. in diameter. The vessel then went through four small, saccular enlargements (ranging from 0.3 to 0.7 cm. in diameter), received a communicating branch from the anterior descending branch of the left coronary, and terminated in a saccular dilatation, 1.6 cm. in diameter, which connected with the pulmonary artery through an opening not quite 2.0 mm. in diameter.

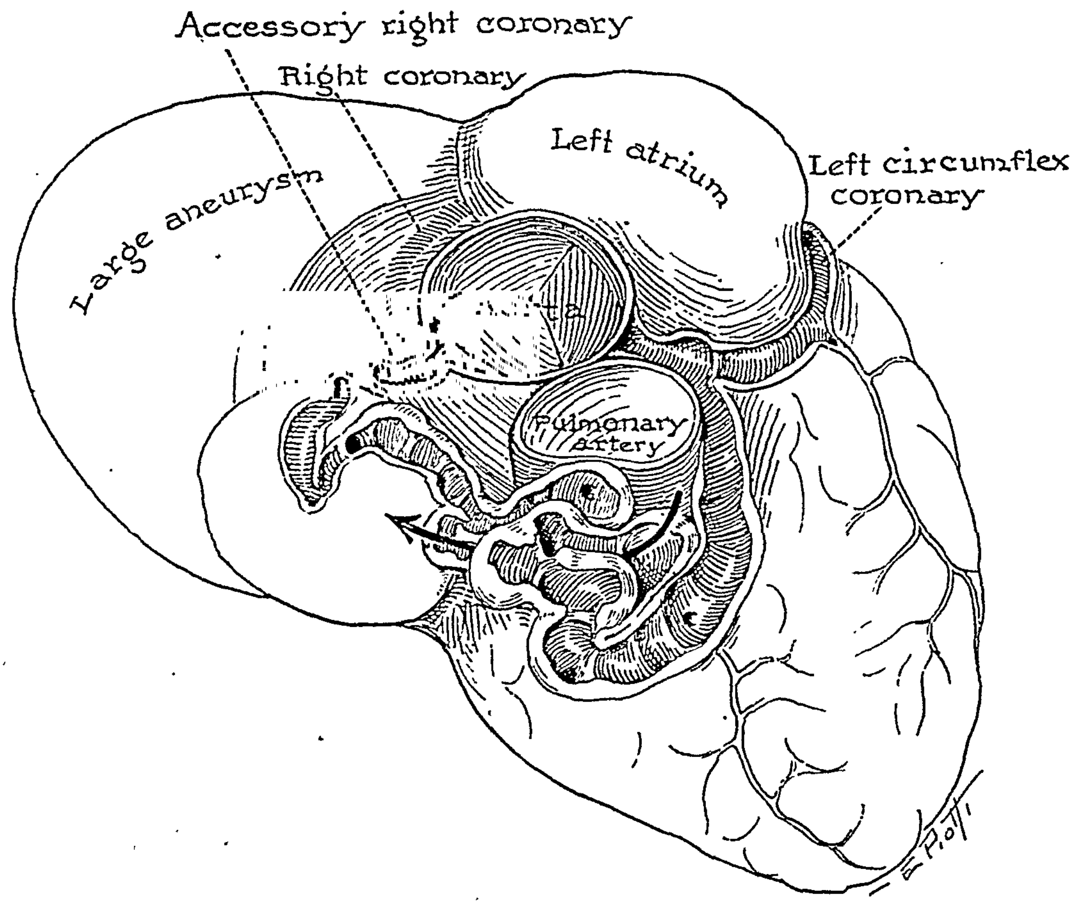

Fig. 6.—(W. L. No. 1,213,451, A46-473). Diagram of anomalous circulation showing connections to all aneurysms. The large aneurysm on the left of the picture overlies the right atrium which is obscured from view.

The left coronary artery proceeded 1.5 cm. from its origin to its point of bifurcation, where there was a small, saccular dilatation 0.8 cm. in diameter. The circumflex branch was not remarkable. The anterior descending branch was dilated to an inside diameter of 0.6 cm., and, 1.8 cm. distally, showed a saccular dilatation 1.1 cm. in diameter, from which two vessels emerged. One was 2.0 mm. in diameter and followed the usual course of the anterior descending coronary. The other was 3.5 mm. in diameter and followed a tortuous course, looping around and beneath itself (Figs. 4 and 6), eventually communicating with the accessory right coronary as has been described. Throughout its course it consisted of a series of localized dilatations with constrictions separating them.

From the origin of the left coronary to the communication with the branch from the right coronary artery, there were ten small dilatations ranging from 0.4 to 1.1 cm. in diameter. There were seven dilatations ranging from 0.3 to 10 cm. in diameter on the accessory right coronary artery. Thus, there were in all seventeen saccular dilatations ranging in size from 0.3 to 10 cm.

in diameter, and all were on the course of the anomalous circulation. These were entirely beneath the epicardium and, with the exception of the two largest, their lumina were patent. There were a few scattered atheromatous plaques on the walls and some of these appeared to be calcified. The walls of the smallest aneurysms were thin and translucent in some areas, measuring less than 1.0 mm. in thickness. The wall of the 3.0 cm. aneurysm was fibrous and calcific, measuring 2.0 mm. thick, and the wall of the 10 cm. aneurysm was fibrous, measuring 1.0 to 2.0 mm. in thickness.

In the remainder of the autopsy significant findings were present in the lungs, genitourinary tract, and the liver. There was also a diverticulum of the duodenum, 3.0 cm. in length and 1.0 cm. in diameter, as well as multiple shallow diverticula of the colon and sigmoid.

The left pleural cavity was completely obliterated by dense fibrous adhesions. The lungs were well aerated in the upper lobes, but both the lower lobes were very moist and firm. The right lung weighed 920 grams and the left, 780 grams. The dependent portions presented a nodular, mottled, reddish-purple appearance from which, on cut section, frothy, pinkish exudate could be expressed.

In the genitourinary tract the remaining prostatic tissue was nodular and firm, measuring 5.2 by 4.1 by 3.0 cm., and was adherent to the rectal wall and bladder wall. The seminal vesicles were shrunken, fibrotic, and hardly distinguishable from the prostate. The prostatic urethra was patent, but its surface was covered with a layer of purulent exudate, The bladder wall was thickened to 0.3 to 1.3 cm. and the lumen was filled with yellow, purulent material. The trigone was ulcerated and covered with exudate. The ureteral orifices were involved in the prostatic mass, but a 2.0 mm. sound could be introduced with some difficulty. Both ureters were dilated, measuring 0.8 cm. in diameter, and the walls were congested and grayish-green in appearance.

The right kidney weighed 260 grams and the left, 300 grams. Both were soft and the surfaces were studded with circumscribed, whitish-yellow masses which showed a tendency to coalesce. On cut section the parenchyma appeared reddish-brown with multiple abscesses measuring up to 1.0 cm. in diameter. There was poor corticomedullary differentiation, the cortex measuring approximately 0.8 cm. in thickness. The pelves and calices were filled with necrotic material which was greenish-yellow on the right and reddish-brown on the left. In the left kidney some of the papillae appeared darker brownish and had a necrotic consistence.

The liver weighed 2,020 grams. On the surface it was not remarkable, but on cut section it showed multiple, poorly defined, irregular areas which were greenish in the centers and shaded through yellowish zones to normal appearing liver tissue. These measured 0.5 to 1.0 cm. in diameter and tended to coalesce, forming irregular, serpentine patterns.

There were no other anomalies found and no other aneurysms. The brain was not examined. The aorta showed very slight atherosclerosis and there was a fibrous connection between the arch of the aorta and the pulmonary artery in the usual location for the obliterated ductus arteriosus.

Microscopic Examination.—Heart: The myocardium showed only a few scattered areas of interstitial fibrosis. The walls of small aneurysms were composed largely of collagenous tissue with fragments of elastica remaining and small deposits of calcium in the subintimal region; there was no muscular tissue. The walls of medium-sized aneurysms were made up of collagenous tissue with deposits of calcium beneath the intima. No elastic tissue and no muscle tissue could be seen and there was no differentiation into layers. There was an organizing thrombus on the surface of intima. The wall of the large aneurysm (10 by 8.0 by 8.0 cm.) was composed of collagenous tissue. No elastic tissue, no muscle tissue, and no differentiation of layers could be seen. Organization of thrombus was present on the surface of intima.

Lungs: In the lower lobes there was peribronchial acute inflammatory reaction extending into adjacent alveoli. The alveoli were partially filled with acute inflammatory exudate and with acidophilic homogeneous material.

Liver: Irregular areas of early necrosis of liver cells surrounded by slight inflammatory reaction, and containing collections of bacteria in the centers were present.

Kidneys: Diffuse, widespread, acute inflammatory reaction involving glomeruli, tubules, and interstitial tissue were present. There was a slight tendency to focal abscess formation. The tubules were moderately dilated. Vessels were engorged and there was intimal thickening of arterioles. There was some extravasation of blood in medullary portions.

Ureters and bladder: The epithelium was destroyed and there was invasion of underlying tissue by polymorphonuclear leucocytes. In some regions of the ureters, this extended through to the periureteral fat.

Prostate: There were irregularly shaped acini with areas of small, irregular cells containing scant cytoplasm and small, dark nuclei. A few mitotic figures and rare gaint cells were seen. There was stromal and perineural invasion by these anaplastic cells. A few scattered foci of acute inflammation were present.

Aorta: The structure was well preserved, with a few typical atheromas beneath the intima. There was no disruption of elastic tissue, even directly below atheromas.

DISCUSSION

This case showed three noteworthy features: the anomalous coronary circulation, the multiple aneurysmal dilatations on this portion of the coronary circulation, and the size attained by one of these aneurysms.

The developmental history of the anomaly is very difficult to analyze. As was shown by Grant,[31] the buds for the coronary vessels begin to develop at the stage of the 11.5 mm. embryo in rabbits, which is at the time the truncus communis is being separated into the aorta and pulmonary artery. Most of the anomalies of coronary circulation reported in the literature (as reviewed by Bland and associates[32]) consist of a displacement of the origin of one or the other of the main coronary arteries. These are easily explained by postulating a slightly abnormal location for the primordial vascular bud. However, in this case there was an abnormal direct communication between the left coronary artery and an accessory right coronary artery; and the common vessel thus formed communicated with the pulmonary artery. It is conceivable that this connection may have served as an accessory ductus arteriosus in embryonic life and persisted. However, there was a well-defined fibrous cord at the usual location for the ductus arteriosus, and it would seem likely that an accessory ductus would be obliterated in much the same manner as the main ductus. A search of the literature fails to reveal any case in which the disturbed circulation of the heart was comparable. The specimen reported by Abbott[3] showed a displacement of the origin of the left coronary artery, the origin being attached to the pulmonary artery and having anastomoses with the right coronary artery. The blood flow was thought to be toward the pulmonary artery in that case.

With the knowledge we have of normal pressure relations in the aorta and pulmonary artery, it is only reasonable to postulate that in this case the flow of blood was toward the pulmonary artery. On the basis of hydrodynamic principles it is further reasonable to postulate a slight actual flow. The friction to be encountered in the course of a vessel this length and having the tortuosity and other obstructions this vessel presented would materially reduce the effective pressure at the site of entrance into the pulmonary artery. This is borne out by the fact that the opening at the pulmonary artery was relatively much smaller than most of the remainder of the vessel. This also gives us a basis for speculating on the development of the aneurysms.

The pressure transmitted from the aorta was opposed by a lesser pressure from the pulmonary artery, but the length of the vessel and its tortuosity tended to equalize these pressures at the level of the pulmonary artery. The result

was an absorption of the aortic pressure by the walls of the anomalous vessel, with dilatation at its weakest points.

The largest aneurysm itself is unique in regard to size. Chiari[10] reported one that was almost as large, but it had a constriction making it somewhat hourglass shaped. In his case the patient died from constriction of the pulmonary artery by pressure from the aneurysm, which led to chronic congestive failure.

The significance of this condition does not seem great when we consider that at no time were there any cardiac symptoms and that the patient survived to the age of 84 years, finally dying from complications of carcinoma of the prostate. In a different location, the aneurysm could have caused symptoms from mechanical effects, as in Chiari's case. With a greater tendency to hypertension, the patient may have died at a much younger age from a rupture of one of these sacculations. There was also the possibility of coronary occlusion from thrombosis in one of the two aneurysms located along the course to the left anterior descending coronary artery. Since none of these occurred, the case is of particular interest as an illustration of the extent to which an abnormality can be present in the heart without causing symptoms.

SUMMARY

1. The literature on aneurysm of the coronary arteries is reviewed.

2. It is suggested that aneurysms of the coronary arteries be considered as either localized or diffuse; and that the localized be further classified into four main groups: congenital, mycotic-embolic, syphilitic, and arteriosclerotic. All diffuse aneurysms of the coronary arteries appear to be on a congenital basis.

3. Using this classification, a total of forty-seven localized aneurysms have been reported since the first report in 1812; and these may be divided as follows: fifteen congenital, twelve mycotic-embolic, six syphilitic, six arteriosclerotic, four of other types, and four unclassified.

4. The common complications of the condition are rupture, thrombosis, and associated myocardial disease.

5. When a localized aneurysm occurs, the left coronary artery is the more frequently involved and the condition is usually single.

6. In a diffuse aneurysm, the right coronary artery is more commonly affected.

7. There are no pathognomonic clinical findings.

8. Men are much more frequently affected than women, particularly in those aneurysms of congenital origin in which the ratio is 14:1.

9. A case is presented in which there were no cardiac complaints in life, and at autopsy there was found an anomalous coronary circulation with multiple aneurysms, the largest of which measured 10 by 8.0 by 8.0 centimeters.

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ATRIAL INFARCTION WITH DIAGNOSTIC ELECTROCARDIOGRAPHIC FINDINGS

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THE purpose of this report is to present a case of myocardial infarction in a 61-year-old man in whom the correct ante-mortem diagnosis of atrial infarction was made on the basis of typical electrocardiographic changes.

Prior to the report of Cushing and associates,[1] the true incidence of atrial infarction was generally unrecognized. Their study showed that the atria were involved in thirty-one (17.0 per cent) of 182 cases of myocardial infarction proved at autopsy. Previous reports[2-4] had indicated a much lower incidence, probably because the atria were not routinely examined adequately and specifically for infarcts. The clinical recognition of atrial infarction is still uncommon, as judged from the paucity of reported cases.[1,3,5,6] The importance of atrial infarction rests on the sequelae, that is, concomitant mural thrombosis in 80 to 84 per cent of the cases,[1,7] with pulmonary thromboembolism in 24 per cent,[8] rupture,[4,9-12] disturbances of conduction which may persist after the acute episode,[6] and arrhythmias such as auricular fibrillation, auricular flutter, and premature auricular beats.[3]

A high incidence of rupture of hemorrhagic infarcts of the atria, especially of the right, has been reported. Clowe and co-workers[9] analyzed fifty-four proved cases and found rupture in right atrium in 70 per cent of them. Krumbhaar and Crowell[4] reviewed 632 reported cases of rupture of the heart; the right atrium was involved in 5 per cent and the left, in 2 per cent. We are reluctant to accept these figures as indicative of the true incidence of atrial rupture, since there were no cases of rupture in the well-studied series of Cushing and associates.[1] It is probable that the incidence of rupture is much lower, because the true incidence of atrial infarction was not realized until recently.

CASE REPORT

H. C., a 61-year-old white man, was admitted to Michael Reese Hospital on Nov. 12, 1946, with the chief complaint of chest pain and syncope. On the morning of admission, while in the Cardiac Clinic, the patient suddenly experienced sharp precordial pain which radiated to the middle of the back. He became nauseated and dizzy, collapsed, and lost consciousness for several minutes.

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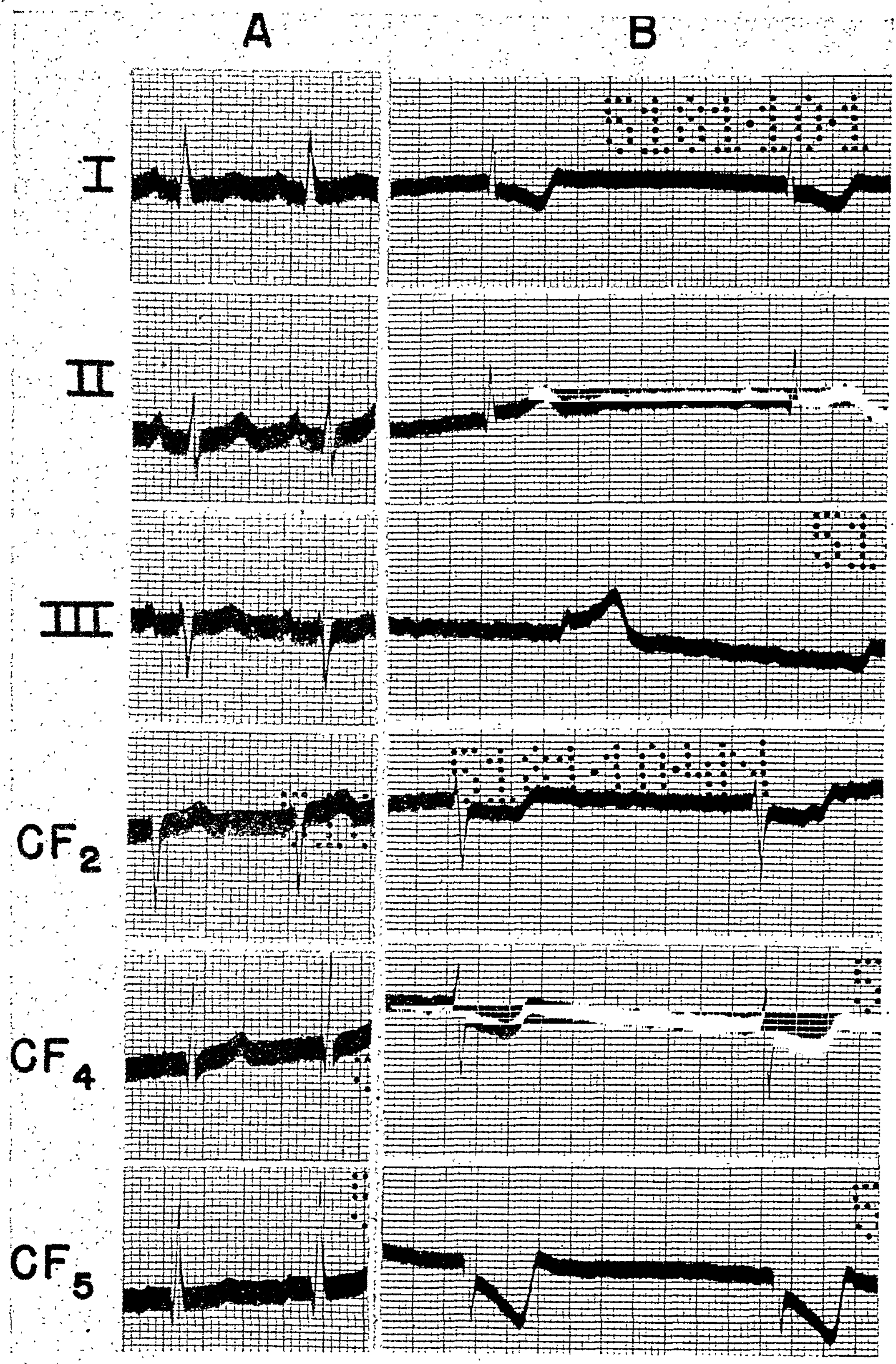


Fig. 1.—*A*, Five months before present illness. Sinus rhythm, left axis shift. *B*, First hospital day. Coarse auricular fibrillation with complete A-V block with the idioventricular pacemaker arising above the bifurcation of the common A-V bundle. Recent posteroseptal infarct.

For the past three years the patient had been treated for hypertension, angina pectoris, and mild diabetes mellitus which had been controlled by diet alone. In 1930, the patient had pulmonary tuberculosis and spent six months in a sanatorium. There were three previous hospital admissions. In October, 1945, he was hospitalized for an acute exacerbation of chronic cholecystitis, fibroid pulmonary tuberculosis, bronchiectasis, and senile emphysema. In February, 1946, he had an hemoptysis. The source was not definitely determined, but it was thought to be from the cavity in the right lung. In May, 1946, the patient was again hospitalized for an exacerbation of chronic cholecystitis. Cholelithiasis was found upon roentgen examination. Cholecystectomy was advised after convalescence.

On admission, the patient appeared acutely ill, cyanotic, and in obvious shock with a cold, clammy skin. The blood pressure was 108/60, the pulse rate was 44, the respirations were 25 per minute, and the temperature was 99.8° Fahrenheit. The pupils were equal and reacted to light and near vision. The neck veins were markedly distended and pulsating. Moist râles were heard in both lung bases. The heart was enlarged to percussion. The heart sounds were distant. No murmurs were heard. The radial pulse was weak, slow, and regular. The liver, kidneys, and spleen were not palpated.

The immediate supportive therapy consisted of morphine, atropine and aminophylline. The blood pressure rose to 174/100 within twelve hours. The pulse rate increased to 90 per minute, and the pulse was of better quality. However, on the second hospital day, the blood pressure again fell and remained in the vicinity of 114/60. On the third hospital day, the pulse rate was 56 and grossly irregular. The patient was conscious and mentally alert throughout his hospital course. The temperature varied from 99.6 to 100.2° Fahrenheit. On the sixth day, the patient suddenly became pulseless and died within several minutes.

Electrocardiograms.—An electrocardiogram made on July 17, 1946 (Fig. 1,*A*), five months before the present illness, showed sinus rhythm and left axis shift. This tracing was considered to be probably abnormal because of the absence of R in Lead CF_2. Fig. 1,*B* shows the electrocardiogram made on the first hospital day; there was coarse auricular fibrillation with complete A-V block, with the idioventricular pacemaker arising above the bifurcation of the common A-V bundle. Changes in the S-T segments and T waves suggested a very recent posteroseptal infarct.

The electrocardiogram shown in Fig. 2,*A* was taken on the morning of the second hospital day. The mechanism now was a regular sinus rhythm with first degree A-V block. Fig. 2,*B* was taken on the evening of the second hospital day. Now there was second degree A-V block with the A-V ratio varying between 3:1 and 3:2. The ventricular rate was 65 per minute, the auricular rate, 100. Changes in the S-T segments and T waves were less marked in all leads.

Fig. 3,*A* shows the electrocardiogram taken on the fifth hospital day. It shows a sinus rhythm and complete A-V block with the idioventricular pacemaker arising above the bifurcation of the common A-V bundle. The elevation of the P-T_A segment in Leads II and III and the changing auricular mechanism were considered compatible with atrial infarction.

The electrocardiogram shown in Fig. 3,*B* was taken twelve hours before death. The ventricular rate is slower in this record. The elevation of the P-T_A segment in Leads II and III persists.

Autopsy.—Post-mortem examination revealed coronary arteriosclerosis with (a) recent thrombosis of the main right coronary artery, (b) old arteriosclerotic occlusion of the left circumflex and left anterior descending rami, (c) massive recent infarct superimposed upon old infarct of the interventricular septum and posterior wall of the left ventricle, with acute fibrinous pericarditis, and (d) recent infarct superimposed upon an organizing infarct of the posterior wall of both atria, with acute fibrinous pericarditis. In addition, there were chronic passive hyperemia of the lungs, liver and kidneys, arteriosclerosis of the kidneys, fibrocaseous tuberculosis of the apex of the right lung, and chronic cholecystitis, pericholecystitis, and cholelithiasis.

The heart weighed 400 grams. The left ventricular wall measured 1.5 cm. in thickness; the right, 0.3 centimeter. The tricuspid ring measured 13 cm. in circumference; the mitral, 9.0 cm.; the pulmonary, 8.0 cm.; and the aortic, 7.0 centimeters. The epicardium on the posterior

aspect was dull and finely granular. The endocardium was smooth and glistening except on the posterior wall of the left ventricle where it was dull, white, and thickened. The myocardium of the posterior wall and upper posterior one-third of the interventricular septum was soft and flabby and was the seat of recent infarction. In this region the pattern of myocardial fibers was poorly outlined, and there were numerous gray and bright yellow friable areas interspersed with hemorrhagic ones. The infarct measured approximately 5.0 by 6.0 cm. and was sharply delineated from the surrounding reddish-brown, firm myocardium.

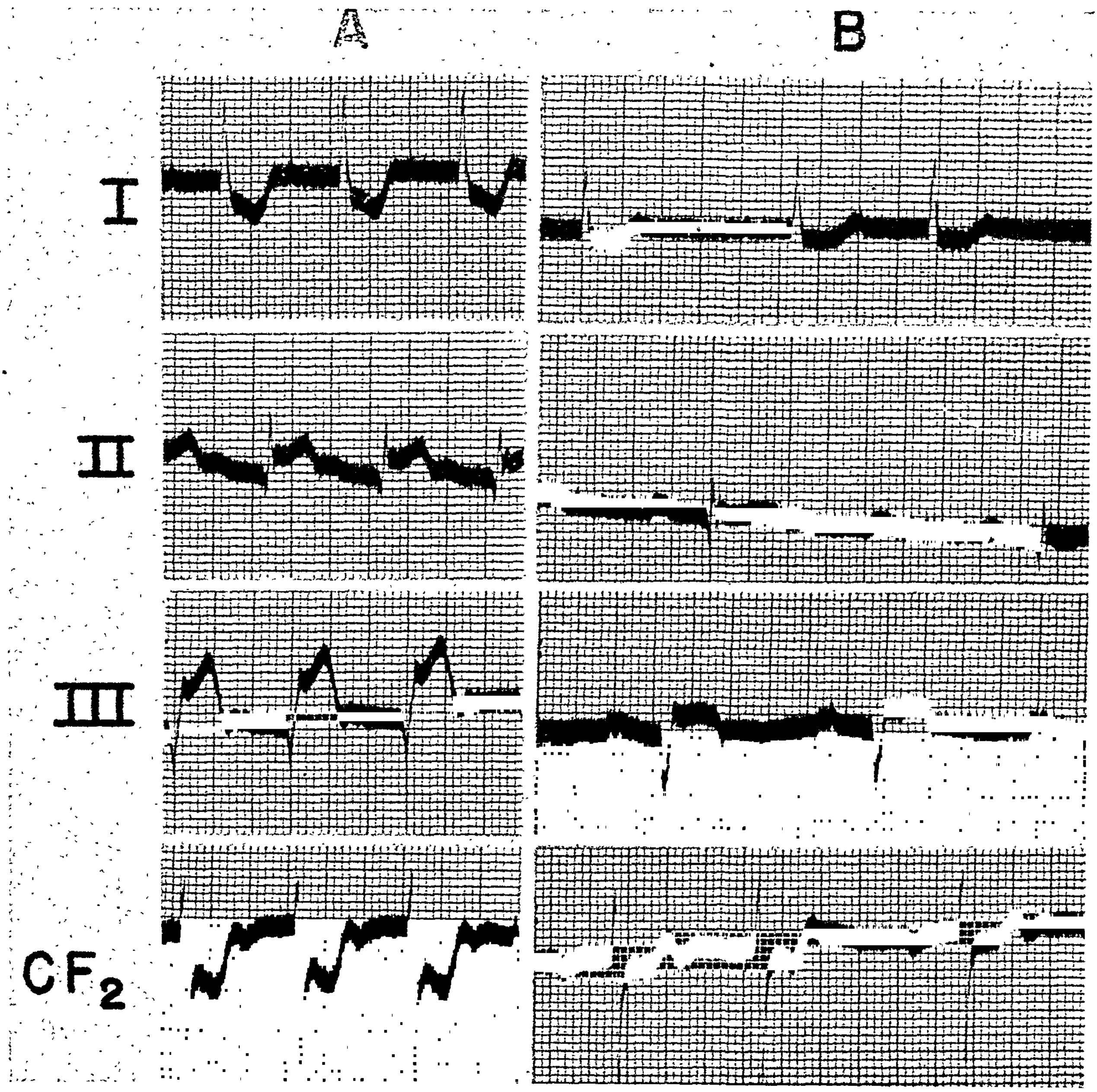


Fig. 2.—*A*, Morning of second hospital day. Sinus rhythm, first degree A-V block. *B*, Evening of second hospital day. Second degree A-V block.

Upon multiple transections of the atria, a soft area was found involving the posterior wall of both atria. The atrial myocardium in this region was friable and red mottled with yellow. This area measured 3.5 by 2.0 cm. and was astride the atrial septum, above and parallel to the auriculoventricular sulcus. Loosely attached to the endocardium in this region were small, red, fibrinous thrombi. The superjacent atrial epicardium was dull, finely granular, and roughened. The right coronary artery was predominant. The coronary arteries were rigid, pipestem, and

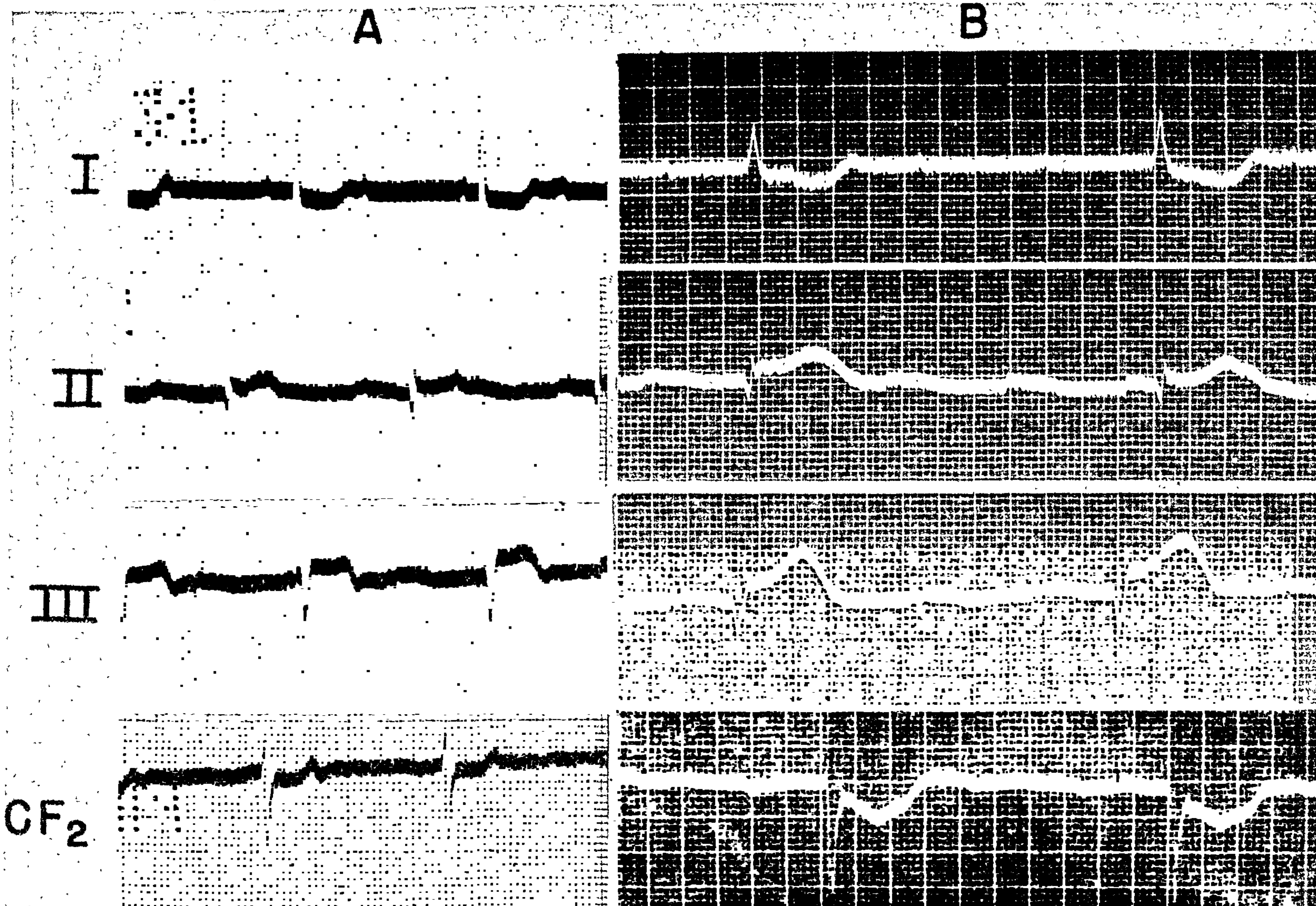
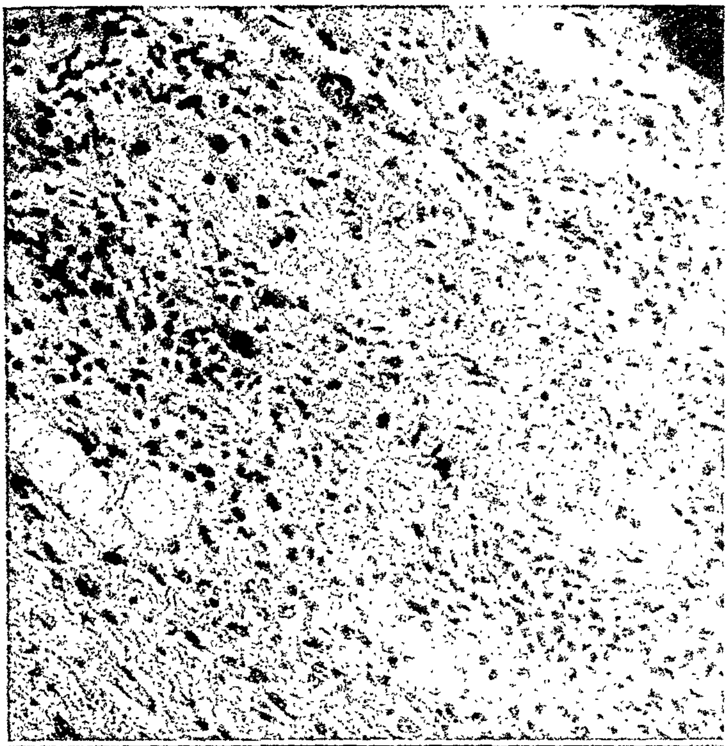


Fig. 3.—*A*, Fifth hospital day. Sinus rhythm. Complete A-V block. Note elevation of P-T_A segment in Leads II and III. Changing auricular mechanism and displacement of the P-T_A segment compatible with atrial infarction. *B*, Twelve hours before death. Elevation of P-T_A segment in Leads II and III persists.

contained numerous arteriosclerotic plaques. The left anterior descending branch was markedly narrowed by a calcific intimal plaque 2.0 cm. below its origin. There was a similar stenosis of the lumen of the left circumflex branch 3.0 cm. from its origin. The lumen of the right main

Fig. 4.



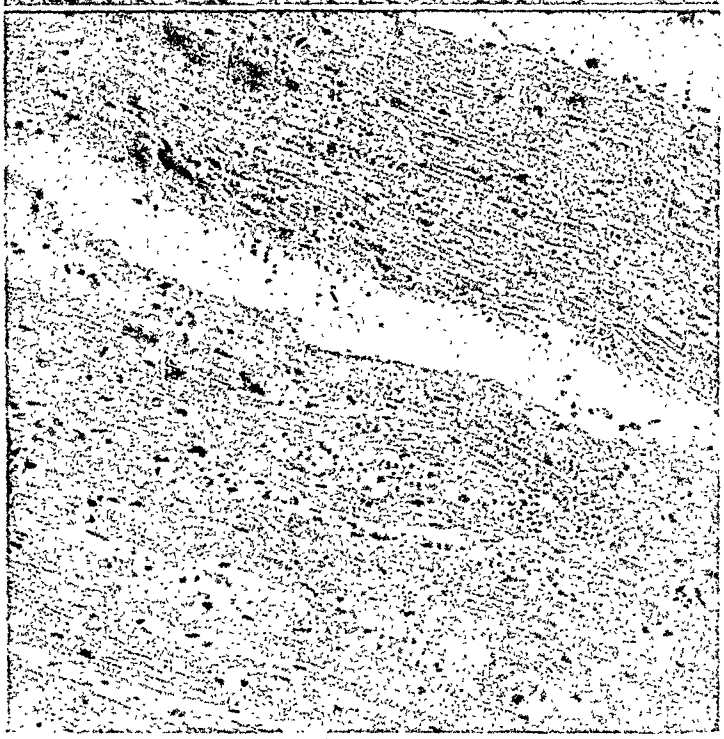


Fig. 5.

Fig. 4.—Photomicrograph (×340). Iron-hematoxylin and eosin. Section of posterior wall of right atrium showing organizing infarct. There is extensive destruction of muscle fibers and replacement by loose fibrous tissue with numerous fibroblasts and round cells. Note also muscle nuclei showing early degenerative changes.

Fig. 5.—Photomicrograph (×170). Iron-hematoxylin and eosin. Section of posterior wall of left atrium showing recent infarct. There is marked segmentation with early loss of cross striations and cloudy swelling. Note dilation of blood vessels with early hemorrhage.

coronary artery was completely occluded by a reddish-brown, recent thrombus 1.0 cm. from its ostium. The aorta was the seat of moderately late severe arteriosclerosis.

Microscopic Description.—Sections of the myocardium of the posterior wall of the left ventricle and interventricular septum were similar. The myocardium showed considerable changes, with large areas in which the sarcoplasm stained poorly and cross striations were absent. In adjacent areas, the architecture of the myocardial fibers was completely destroyed and obscured by local hemorrhage and exudation of polymorphonuclear leucocytes, many of which showed phagocytic activity. In some sections the infarct showed organization, with new formation of numerous capillaries and young fibrous connective tissue. The pericardial adipose tissue was diffusely infiltrated with polymorphonuclear leucocytes. The epicardium was covered with a loose network of fibrin, enmeshing numerous polymorphonuclear leucocytes.

Sections of the posterior wall of both atria were similar (Figs. 4 and 5). Acute fibrinous pericarditis was also present. In the vicinity of organizing infarction, there were areas in which the myocardial fibers had lost their cross striations and nuclei and had a congealed appearance. Between these fibers there were areas of recent hemorrhage. One section revealed a recent mural thrombus with early organization of the base. Section of the right coronary artery revealed the lumen to be completely occluded by a recent thrombus attached to an intimal plaque.

DISCUSSION

The presence of atrial infarction was correctly anticipated, ante mortem, on the basis of a disturbed auricular mechanism and abnormal contour of the auricular complex in a patient with a typical clinical picture of ventricular myocardial infarction. The coexistence of second and third degree A-V block facilitated the recognition of the displacement of the P-T_A segment. Cushing and associates[1] found abnormalities in the auricular mechanism of the electrocardiogram in 74 per cent of cases of atrial infarction, but in only 9 per cent of all cases of "pure" infarction of the ventricle. These abnormalities included auricular fibrillation, auricular flutter, premature auricular beats, paroxysmal auricular tachycardia, sinus arrest, wandering pacemaker, and A-V nodal rhythm. Similar arrhythmias have followed various types of experimental atrial injury, that is, by cautery, by alcohol injections, and by ligature of atrial arteries.[1,13] Clinically, these arrhythmias are usually transient, but may persist for years.[6,18] Perelman and Miller[6] recently reported the case of a 52-year-old man with myocardial infarction who had multiple disturbances of rhythm and conduction, auricular flutter, fibrillation, and first, second, and third degree A-V block which persisted for three years. Although an autopsy was not performed, the authors felt certain that there was an atrial infarct.

Although there is usually an associated infarction of the ventricle as in our case and in twenty-three of the thirty-one cases of Cushing and associates[1] and in fourteen of Wartman's seventeen cases,[7] atrial infarction may occur alone, or in hearts with hypertrophy or myocarditis.[1] Auricular fibrillation was the most common disturbance of the auricular mechanism in solitary atrial infarction in the series of Cushing and associates.

The posterior location of the atrial infarct and the abnormalities of the contour of the auricular complex are of particular interest in our case. The posterior atrial wall is not commonly involved. Infarction occurred in this location in only three of thirty-one cases.[1] The occurrence of elevation of the

P-R segment (designated as the P-T_A segment by Abramson and associates[14]) in Leads II and III is unusual. We have found no other case reported with similar P-T_A elevation in Leads II and III.

The direction of the P-T_A deviation should depend upon the location of the infarct, in a manner analagous to the S-T deviations in ventricular infarction. Theoretically, injury of the subepicardial myocardium of the posterior basal wall should result in positive deviation of the P-T_A segment in Lead III, usually in Lead II, with negative displacement in Lead I. When the location is anterior or anterolateral, one would anticipate depression of P-T_A in Lead III and elevation in Lead I.[19,20] Such P-T_A depression occurred in Leads II and III in infarction of the right atrial appendage in the cases of Cushing and associates[1] and of Langendorf.[5] Anatomically, the right atrial appendage lies in an anterior or anterolateral position. The high incidence of right atrial appendage infarction as compared with the left atrial involvement has been emphasized. Hence, the rarity of P-T_A elevation in Leads II and III is due to the uncommon involvement of the posterior wall of the atria. In cases of uremia with diffuse fibrinous pericarditis, displacement of the P-T_A segment has not been noted, although characteristic RS-T and T-wave changes occur when the subepicardial myocardium is involved. It is possible that P-T_A displacement occurs when the atria are involved but is undetected. The occurrence of A-V block, as in our case, facilitates the recognition of such deviation.

The clinical recognition of atrial infarction has practical significance. The immediate consequence of atrial involvement is mainly that of a disturbed rhythm, which may precipitate congestive failure if an already damaged heart is subjected to prolonged rapid action. The immediate control of such arrhythmias, if possible, is mandatory.

The subsequent sequelae of atrial infarction include mural thrombosis with thromboembolism, and rupture. Mural thrombi were found adherent to the endocardium over the area of infarction in 84 per cent of the cases of atrial infarction. A similar incidence was noted by Wartman and Hellerstein[7] of which twenty-four per cent showed pulmonary embolism and infarction. The use of anticoagulants would therefore appear logical in atrial infarction, in view of the favorable reports on the value of anticoagulant therapy in the prevention of mural thrombosis and thromboembolism in ventricular infarction.[15-17]

SUMMARY

A case of atrial infarction in a 61-year-old man is presented in which the correct ante-mortem diagnosis was made. Serial electrocardiograms showed a changing auricular mechanism with coarse auricular fibrillation, varying degrees of A-V block, and elevation of the P-T_A (P-R) segment in Leads II and III.

The clinical recognition of atrial infarction, which is more common than generally believed, is important because of the complications of arrhythmias, mural thrombosis, thromboembolism, and rupture.

I am pleased to acknowledge the valuable suggestions and advice of Dr. L. N. Katz and Dr. R. Langendorf. I am indebted to Dr. W. Brams for his permission to present this case and to Dr. O. Saphir for the pathological report and photomicrographs.

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SEPTAL INFARCTION WITH COMPLETE HEART BLOCK AND INTERMITTENT ANOMALOUS ATRIOVENTRICULAR EXCITATION (WOLFF-PARKINSON-WHITE SYNDROME): HISTOLOGIC DEMONSTRATION OF A RIGHT LATERAL BUNDLE

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THE most widely accepted explanation of the syndrome of anomalous atrioventricular excitation, and most particularly of the Wolff-Parkinson-White syndrome, is the presence, in addition to the atrioventricular bundle of His, of a functioning anatomic bridge of cardiac muscle from atrium to ventricle of the type described by Kent.[1-5] The existence of such anomalous bundles is said to be uncommon in childhood, rare in adults.[6,7] Structures of this type have been found* on careful serial microscopic examination of the atrioventricular groove in patients with the syndrome. The impulse is apparently conducted over the anomalous bundle sooner than over the atrioventricular bundle, and the activation of the ventricle is eccentric, producing in the typical Wolff-Parkinson-White syndrome a short P-R interval with prolongation of the QRS complex. The difficulty of diagnosing myocardial infarction in such patients[10] has been pointed out,[11,12] and the possibility of making this diagnosis on other than clinical grounds has even been denied.[13] Zoll and Sacks,[14] however, have reported a patient with myocardial infarction whose electrocardiograms showed, in addition to short P-R and prolonged QRS complex, typical coving and inversion of T_2 and T_3. The patient recovered. In view of this patient's history of frequent attacks of paroxysmal tachycardia, these authors considered that the anomaly probably antedated the attack of myocardial infarction. In the case which we are reporting, a clinical diagnosis of septal infarction with intermittent anomalous conduction was made, and post-mortem examination showed massive myocardial infarction involving the septum and the posterior portion of the left ventricle. Further studies revealed the presence of a right lateral bundle.

CASE HISTORY

Mrs. G. V., a 62-year-old widow, was admitted to the Peter Bent Brigham Hospital on June 22, 1947, because of precordial aching, nausea, and vomiting beginning eighteen hours before admission, and coma beginning five hours before admission. The history was obtained from the

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*Because the complete serial examination of the atrioventricular groove in even a single case is so laborious and time-consuming, the number of such studies reported is quite limited. Study of a much larger group of normal hearts is desirable to evaluate the significance of accessory bundles in cases of short P-R interval with prolonged QRS complex.

patient's daughter who had lived away from the patient for a number of years and was uncertain of the details of her mother's health. The patient had, so far as her daughter knew, always been in good health with no complaints or difficulties prior to the present illness.

Physical examination on admission showed an obese, flaccid, unresponsive woman in coma, whose respirations were deep and stertorous. The maximum impulse of the cardiac apex could not be felt. The left border of cardiac dullness appeared to be in the left mid-clavicular line. Being almost synchronous with respiration, the heart sounds were very difficult to hear. The blood pressure, which could be recorded only by the method of palpation, was 60 mm. Hg, systolic. The radial pulse rate was 52 beats to the minute. The lungs were clear, and there was no evidence of congestive heart failure. Neurological examination showed evidence of focal disturbance in the central nervous system, the details of which are not germane to this discussion.

Electrocardiographic examination was carried out shortly after admission. For the most part, the tracings (Fig. 1) showed complete atrioventricular heart block, the atrial rate being 103, and the ventricular, 52 beats to the minute. This rhythm was noted in all but the third complex in Lead I, in the first three complexes in Lead II, and in the last three in Lead III. The ventricular complex during the periods of complete heart block lasted 0.14 second and conformed either to a right bundle branch block or to an idioventricular rhythm with the pacemaker below and to the left of the common atrioventricular bundle. The heart was in the horizontal electrical position. The conventional leads showed a depression of $S\text{-}T_1$, elevation of $S\text{-}T_2$ and $S\text{-}T_3$, and late inversion of T_2 and T_3 of the coronary type. Unipolar limb leads showed a depressed S-T in Lead aV_L, deep Q, elevated RS-T, and late inversion of T in Lead aV_F. Unipolar chest leads during the period of complete block showed late intrinsic deflection in Leads V_1 through V_4, early intrinsic deflections in Leads V_5 and V_6, deep Q in Leads V_1 through V_3, and deep Q, elevated RS-T, and late inversion of T in Lead V_4. The last three complexes in Lead II and the first three in Lead III, on the other hand, showed atrioventricular conduction with short P-R interval (0.10 to 0.12 second), increased QRS duration (0.14 second), no Q waves, but the same late inversion of the T waves. This indicates that the ventricles were invaded by the electrical impulse in different ways, depending upon whether the impulse was or was not conducted from the atrium, but that electrical regression was the same in either case. The P waves, whether or not conducted, were low, almost isoelectric, notched, and prolonged in Leads II and III. Isolated beats showing short P-R intervals and a different form of ventricular complex were also recorded in Lead I (third complex), in Lead aV_R (first complex), in Lead aV_F (second complex), in Lead V_2 (second complex), and in Lead V_3 (second complex), these conducted impulses breaking up the slow idioventricular rhythm. The atrial and ventricular rates during the period of atrioventricular conduction were 55 beats to the minute.

Other routine laboratory examinations were not remarkable. The patient failed to rally, remained comatose, became cyanotic, and died five hours after admission.

Post-mortem Examination.—At autopsy the entire interventricular septum and posterior portion of the left ventricle near the apex were infarcted. The myocardium in these infarcted areas was soft and spongy and dark greyish-yellow centrally. About the periphery of the infarct numerous petechiae were seen. Other gross findings were cardiac enlargement (420 grams), mural thrombus along the interventricular septum in the left ventricle, normal heart valves, and marked arteriosclerotic narrowing of the coronary arteries without fresh thrombosis.

Microscopic examination showed extensive fresh infarction of the myocardium in the regions of infarction described grossly. This is illustrated in Fig. 2 which is a transverse section taken across the interventricular septum just beneath the "undefended space" of the heart, which is the area through which the atrioventricular bundle passes. Scattered throughout all sections were small areas of fibrosis regarded as evidence of long-standing coronary insufficiency.

Serial microscopic sections were also taken of a block of tissue from the right posterolateral aspect of the heart along the atrioventricular groove including 1.0 cm. of atrial and ventricular muscle on each side of the groove. Every fifth section was stained with Masson's trichrome stain. These sections (Figs. 3 and 4) showed a band of healthy cardiac muscle bridging the fibrous and fatty tissue of the atrioventricular groove (Fig. 3) continuous with the ventricular muscle (Fig. 4). Technical difficulties prevent us from reproducing a complete connection between the bundle and

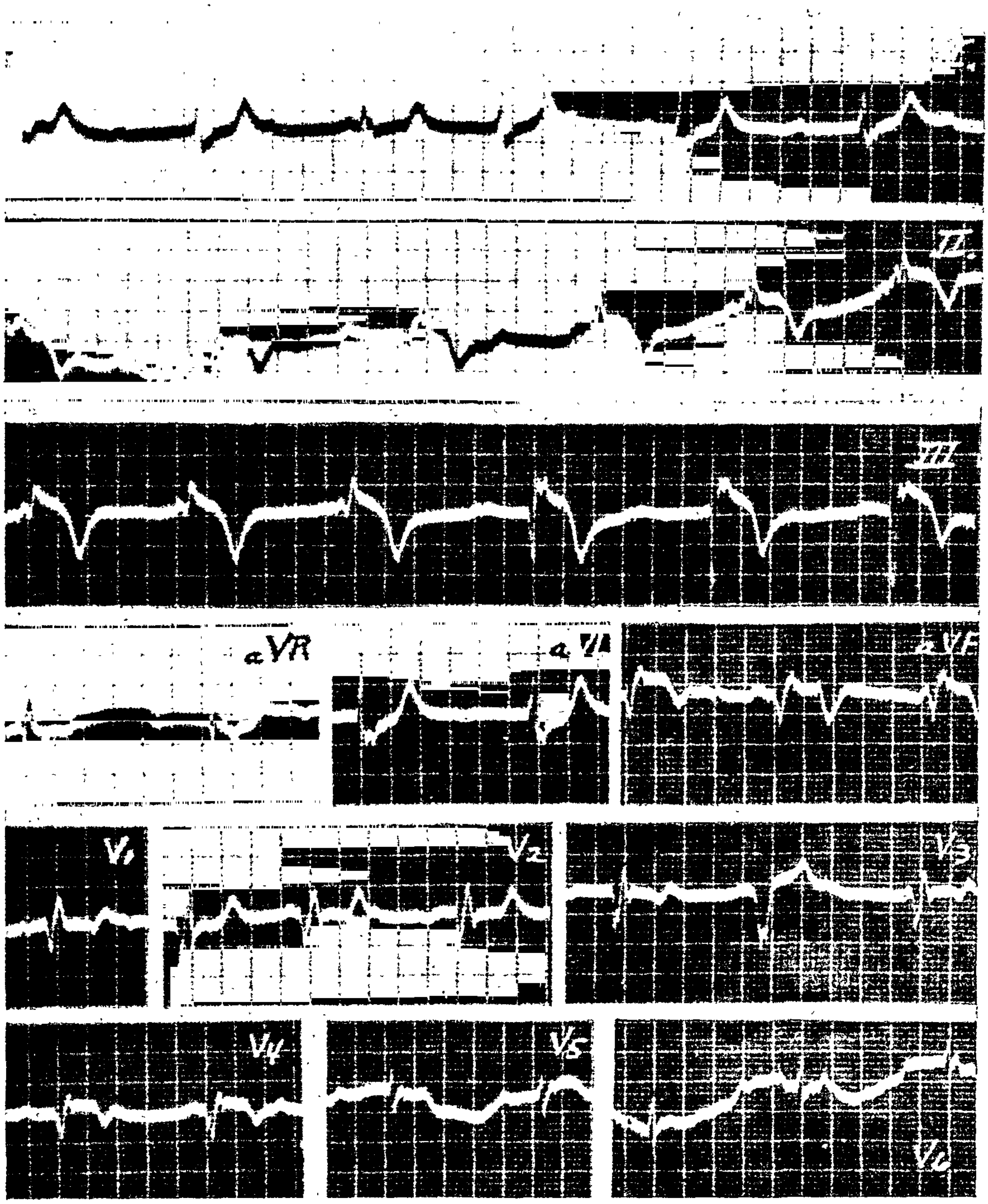

Fig. 1.—Twelve lead electrocardiograms showing complete heart block with a ventricular rate of 52 and an auricular rate of 103. Heart in horizontal electrical position. S-T_1 is depressed and S-T_2 and S-T_3 are elevated. There is late inversion of T_2 and T_3 with coronary contour. The first three complexes in Lead III show atrioventricular conduction, but the P-R interval is only 0.10 second. The deep Q shown in the following three dissociated ventricular complexes is not present in these conducted impulses, indicating a different method of invasion of the ventricle by the impulse. The heart rate during atrioventricular conduction is 55 per minute. Isolated beats showing atrioventricular conduction with short P-R interval are seen in Leads I, aV_R, aV_F, V_2, and V_3 where they interfere with the slow idioventricular rhythm. The QRS interval during block and during atrioventricular conduction was 0.14 second. The intrinsic deflection is late in Leads V_1 through V_4, early in Leads V_5 and V_6. Thus, either right bundle branch block is present or there is an idioventricular rhythm with a pacemaker below and on the left ventricular side of the common atrioventricular bundle. Q waves are present in Leads V_1 through V_6. These tracings were regarded as characteristic of posterior myocardial infarction. The complete heart block and the possible right bundle branch block were regarded as very suggestive of septal infarction and the periods of rapid atrioventricular conduction of the presence of a functioning collateral atrioventricular bundle.

the auricular muscle, but the nature of the bundle and its deep penetration into the auricular tissue leave no doubt of their continuity.* Further studies of the atrioventricular groove to demonstrate the possible presence of additional muscular connections between the atria and ventricles were not undertaken.

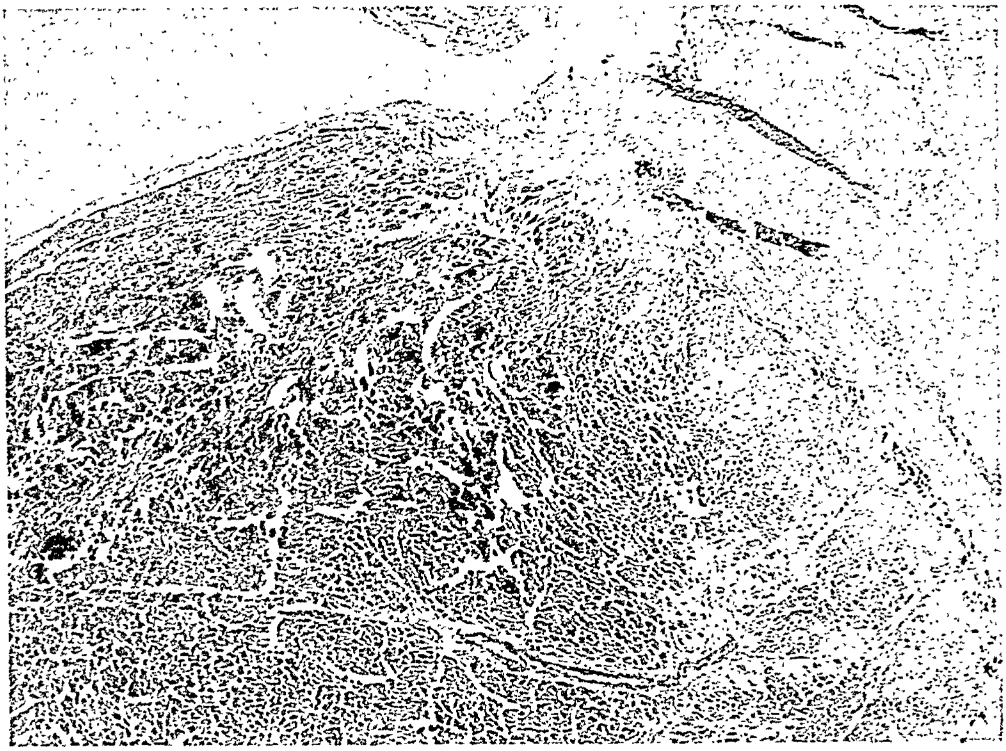

Fig. 2.—Hematoxylin-eosin section of basalar portion of interventricular septum (×45) with fibrous "undefended space" just above and to the right. Extensive fresh infarction of myocardium in region through which atrioventricular bundle (His) courses, a pathological basis for complete heart block.

DISCUSSION

This case is remarkable in many respects. (1) A clinical diagnosis of myocardial infarction was made in the face of anomalous conduction and was confirmed at post-mortem examination. The available literature contains no reference to a similar case. (2) An accessory bundle was suspected from the electrocardiographic pattern and found on careful microscopic examination of the atrioventricular groove. (3) Involvement of the interventricular septum, and particularly of its upper portion, the site of the atrioventricular bundle, was postulated from the presence of complete heart block and confirmed at necropsy. (4) Experience[15-19] has shown that certain pharmacologic agents (atropine, digitalis, quinidine, epinephrin) or physiologic procedures (exercise, change in position, carotid sinus pressure) can cause the impulse to be conducted down the path of least resistance, be it the atrioventricular or the anomalous bundle. In the present case a pathologic process, myocardial infarction, produced com-

*This is not only the conclusion of the authors, but also the conclusion of pathologists whose opinion was sought. We regret that in cutting the sections several important ones were lost.

Fig. 3.

Fig. 4.

Fig. 3.—Section from right posterolateral aspect of atrioventricular groove. Masson's trichrome stain (×45). Bridge of healthy cardiac muscle extending across fibroareolar tissue of atrioventricular groove, an anatomical basis for aberrant atrioventricular conduction. Muscle of right auricle at upper left, of right ventricle at lower right. Tricuspid valve, lower left.

Fig. 4.—Same, thirty-five sections beyond section shown in Fig. 3, demonstrating continuity of bridge with ventricular muscle.

plete block in the normal atrioventricular bundle so that the ventricles either beat at their own inherent rate or were activated by impulses traversing the healthy anomalous bundle. This represents a nice anatomical-physiological correlation and is quite consistent with the hypothesis of an aberrant pathway as the explanation for the syndrome of short P-R interval with prolonged QRS complex.

The location of the anomalous bundle (Figs. 3 and 4) in the present case corresponds to that described in the anatomical studies of Kent[5] and to the physiological studies of Rosenbaum and associates[18] in that ventricular activation must proceed from the subepicardial to the subendocardial layers of the heart rather than in the normal subendocardial to subepicardial direction.

In this case the RS-T segment deviation and the coronary type of T-wave inversion were present during both normal (or relatively normal) and anomalous ventricular excitation, whereas the QRS changes (small Q_2, deep Q_3) were noted only during normal excitation. It seems, then, that in the syndrome of short P-R interval, prolonged QRS complex with posterior myocardial infarction, the change in the initial ventricular complex may be obliterated when the ventricles are stimulated via the anomalous pathway but the changes in the final deflection persist.* Thus, the diagnosis of posterior myocardial infarction in the presence of constant anomalous conduction[14] must depend upon changes in the RS-T segment and in the T wave. If, however, some of the impulses pursue normal or relatively normal pathways, QRS changes may be noted as well.

SUMMARY

A proved case of myocardial infarction involving the interventricular septum showed complete heart block and intermittent anomalous atrioventricular excitation (short P-R interval, prolonged QRS complex). At necropsy an accessory right lateral bundle was found bridging the atrioventricular groove at the right posterolateral aspect of the heart. In this case anomalous ventricular excitation obliterated the QRS changes of posterior myocardial infarction, but the RS-T and T-wave changes persisted.

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*When the free wall of the ventricle (septal activation being neglected) is activated from the endocardial to the epicardial surface, a deep downward deflection (Q wave) is recorded in the ventricular cavity; an electrode overlying a transmural infarct of this free wall, therefore, records a Q wave. On the other hand, when the free wall of the ventricle is activated from the epicardial to the endocardial surface, an initial upward deflection is recorded in the ventricular cavity; therefore, an electrode overlying a transmural infarct of the free wall no longer records a Q wave.

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Clinical Reports

CONGENITAL TRICUSPID ATRESIA ASSOCIATED WITH INTERAURICULAR AND INTERVENTRICULAR SEPTAL DEFECTS

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RECENT advances in cardiac surgery offer hope that more can be done for cases of congenital heart disease. This presupposes accurate clinical recognition of the various complexes. The following case is an example of one of the rarer anomalies, but the picture is typical and it is hoped that this report will help others to recognize this congenital malformation during life.

CASE REPORT

M. B., a white female child, was cyanotic at birth and had moderate respiratory difficulty. An apical systolic murmur and precordial systolic thrill led to the diagnosis of congenital heart disease, but the cyanosis cleared up within a few days and did not reappear until several months later.

She was readmitted to the hospital at the age of 4 months because of a persistent upper respiratory infection and frequent vomiting. At home she had been vomiting occasionally for about four weeks, but she was well nourished and her weight was normal. With the onset of the recent acute symptoms, the mother had noted persistent mild cyanosis. The temperature on admission was 102° F., and roentgenogram of the chest showed bronchopneumonia. She responded to treatment and was discharged, but after this episode the dyspnea and cyanosis were persistent and increasingly severe, requiring frequent administration of oxygen.

At the age of 3 years, 4 months, the child developed an acute tonsillitis and otitis media. She was treated at home with sulfadiazine and penicillin and seemed to be improving, but several generalized convulsions caused her to be readmitted to the hospital. She seemed acutely ill and had a temperature of 101° Fahrenheit. Physical examination showed extreme cyanosis, clubbing of the fingers and toes, and moderately injected eardrums. The heart was enlarged and there was a strong precordial pulse and thrill. There was a systolic murmur, loud and machinelike in character, and a faint presystolic murmur, both maximal in the third intercostal space at the left sternal border. A high-pitched systolic murmur of a different character was heard best in the pulmonic area. The pulse was regular and rapid. The electrocardiogram showed left axis deviation. An x-ray film of the chest (Fig. 1) showed left ventricular hypertrophy.

The urine was negative except for many white blood cells in the sediment. A urine culture showed *Staphylococcus albus*. The red blood cell count was 5,900,000 per cubic millimeter, the white blood cell count was 13,500 per cubic millimeter, and the differential showed 85 per cent

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segmented polymorphonuclear leucocytes, 13 per cent lymphocytes, and 2 per cent mononuclear cells. The sedimentation rate was 6 mm. in one hour.

In spite of the administration of sulfadiazine and penicillin, the temperature remained elevated. Soon there appeared an outward deviation of the right eye and weakness of the left

Fig. 1.—Roentgenogram of the chest showing the typical cardiac silhouette. Note the absence of the shadow normally cast by the pulmonary conus.

Fig. 2.—Looking down into the right auricle. The arrow points to the atresic tricuspid orifice. Below is the interauricular septal defect.

arm and leg. Examination revealed positive Babinski and Chaddock signs bilaterally, hyperactive deep reflexes, a left pupil which was larger than the right, and bilateral choking of the optic discs. The presumptive diagnosis of subacute bacterial endocarditis with cerebral embolism and abscess formation was made, but numerous blood cultures failed to reveal the expected bacteremia. The white blood cell count rose steadily to 50,000 cells per cubic millimeter, as did

the fever, which terminally measured 106° Fahrenheit. In spite of intensified penicillin therapy, the child became comatose and died following the onset of cardiac decompensation.

Necropsy.—A complete necropsy was performed, but only the main lesions will be reported. Aside from generalized congestion of the viscera, cyanosis of mucous membranes, and clubbing of the fingers and toes, the findings of interest are limited to the heart and brain.

Fig. 3.—Left auricular aspect showing the interauricular septal defect and the hypertrophied left ventricle.

Fig. 4.—Showing the interventricular septal defect.

Heart (Figs. 2, 3, and 4): The weight was 120 grams (normal weight, about 70 grams). The epicardium was smooth and glistening. The epicardial fat was normal. The preponderance of weight was on the left side, which was very firm. The right auricle showed the endocardial surface to have many fibrous trabeculae. When opened it appeared larger than normal, measuring 8.0 cm. in circumference. Where the tricuspid orifice should have been, there was only a

depressed fibrous dimple. There was an interauricular septal defect measuring 2.0 by 1.0 centimeter. The right ventricle, which was not directly connected with the right auricle, was very small, although the wall was thick (8.0 mm.). The pulmonary leaflets were more fibrous than normal, the pulmonary ring measured 3.5 cm. in diameter, and the pulmonary artery was normal. The ductus arteriosus was closed. The left auricle was large, measuring 8.0 cm. in diameter. The mitral valve was normal and measured 7.5 centimeters. The left ventricular wall measured 14 mm. in thickness. Behind the mitral valve, there was an interventricular septal defect measuring 1.5 by 1.0 centimeter. The aortic valve was normal, and the aortic ring measured 3.5 centimeters. The root of the aorta was normal. The coronary arteries were normal.

Brain: The dura was normal. When the brain was exposed, the right hemisphere was found to be soft and fluctuant, as was the occipital lobe of the left hemisphere. Coronal sections showed a large abscess, 4.0 by 5.0 by 5.0 cm. in the frontal lobe on the right, and a similar abscess in the occipital lobe on the left. There was much exudate over the pia-arachnoid on both sides.

Middle Ear: The middle ear on the right contained creamy pus. The left was normal.

Final Anatomic Diagnosis: Congenital tricuspid atresia; septum primum with ostium atrioventriculare commune; interventricular septal defect; chronic otitis media, right side; brain abscesses, multiple.

DISCUSSION

This case illustrated accurately both the clinical and anatomic findings.

Clinically the picture is clear and, in retrospect, not to be confused with that of other congenital anomalies. In the cyanotic group this is the only lesion which gives a left axis deviation of the electrocardiogram and is thereby easily distinguished from cases of tetrology of Fallot. Furthermore, the roentgenogram of the cardiac silhouette is characteristic in that there is an absence of the convexity normally cast by the pulmonary conus, and a slight concavity in this region is usual (Fig. 1). These two findings should enable one to make a diagnosis regardless of the murmur present.

As a matter of fact, murmurs are not diagnostic in this syndrome, many varieties having been described in the reported cases. It is easy to see that the abnormal intracardiac course of the blood depends on the associated lesions, and particularly on the relative size of the interauricular and the interventricular defects. In one case[14] no murmurs were present in spite of extreme anatomic defects.

Anatomically this case is typical of the majority of cases reported. Although various associated abnormalities are reported, the simplest and most common is illustrated by the defects in the interauricular and interventricular septum; such defects are necessary to surmount the atresia of the tricuspid valve. In the absence of a patent ductus, the interventricular defect is of course necessary.

Although it is said that fetal endocarditis is sometimes the cause of the atresia, histologic sections through the atretic area failed to show any signs of inflammatory disease. The mechanical explanation is more likely. If the endocardial cushions, which are the anlage of the valve leaflets, hypertrophy and fuse so as to shut off the normal valve opening, the blood flow would prevent the closure of the ostium primum, and, similarly, there would be a failure of the interventricular ostium to close. Since in the complex here described there was no transposition of the vessels, the atresia can be assumed to have occurred

before the eighth week, when the septa closed, and after the obliteration of the right-sided aorta.

Tricuspid atresia is relatively rare. In Abbott's[1] series of 1,000 cases, twenty-five instances of tricuspid atresia are listed. We have been able to find reports of an additional fifteen cases.[2-15]

SUMMARY

1. A case of congenital tricuspid atresia with associated defects is presented.
2. The clinical picture is typical and easily distinguishes this condition from other congenital malformations in the cyanotic group.
3. This is the forty-first reported case.

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GANGRENE OF LOWER EXTREMITIES IN INFANTS

Report of Two Cases

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Arterial occlusion with gangrene of extremities is commonly encountered in adults and is usually due either to embolism or disease of the vessel wall. Gangrene of extremities in infants, however, is very rare. In 1945, Gross[1] reported six cases of his own and reviewed forty-one other reported cases. A similar review was made in 1941 by Heller and Alvari.[2] Von Khautz,[3] in 1914, reported a group of fifty cases of gangrene in children varying in age from newborn to 15 years of age. Of these fifty cases, thirty-nine occurred after or during acute infections such as diphtheria, typhoid, scarlet fever, pneumonia, and so forth. Of the fifty cases reported in this series, twenty-one recovered, sixteen died, and the outcome of thirteen cases was not known. Because of the rarity of gangrene in infants we feel that the report of two cases, with necropsy findings in one case, may be of interest.

CASE REPORTS

Case 1.—M. H., a 3½-month-old white boy, was admitted to the Coney Island Hospital on Nov. 3, 1946, with a history of fever beginning on the sixth day of life and followed by diarrhea and vomiting. The family history revealed that two other male children previously had suffered from a similar condition, consisting of fever of unknown origin and diarrhea.

On admission the child was vomiting and had severe diarrhea. Physical findings were essentially negative. While the infant was in the hospital the temperature was elevated most of the time, ranging from 100° to 108° F.; on occasional days the temperature was normal.

X-ray examination of chest and abdomen, urine examination, and blood studies were negative. Blood count revealed hemoglobin, 13 grams; red blood cells, 4,830,000; white blood cells, 4,800, with 40 per cent polymorphonuclear leucocytes, 45 per cent lymphocytes, and 15 per cent monocytes. Basophilic stippling was present. The platelets were normal. Treatment consisted of several transfusions, change of feeding formula, and penicillin, without any apparent improvement.

On the sixteenth hospital day evidence of disturbed circulation in the lower extremities appeared. There was a patchy cyanosis and edema of the right leg and foot extending to a level slightly below the knee. There were several areas of necrosis of the left leg and foot involving the areas where incisions were made for transfusions and where bone marrow transfusion in the left tibia had been given. There were several areas of necrosis and ecchymosis on the left thigh and gluteal region where penicillin was injected. Both feet and legs were cold to touch, the right

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being colder. Pulsations of both femoral arteries were normal but pulsations of both the dorsalis pedis and posterior tibial arteries were absent. Oscillometric readings made on both thighs were absent. Heparin was given intravenously, after which the color and temperature of the right leg and foot improved except for dry gangrene of the first three toes. The necrotic areas on the left lower extremity were unaffected. The patient died on Nov. 27, 1946. The final clinical diagnosis was, "Fever of unknown origin and thrombosis of both femoral arteries." Autopsy was not obtained.

CASE 2.—A. M., a 2-year-old white girl, was admitted to the Coney Island Hospital because of temperature, cough, and difficult breathing. Examination on admission revealed a pale, acutely ill, mentally and physically retarded baby. Coarse râles were scattered throughout both lung fields. There was no dullness present. The pharynx was mildly inflamed. The diagnosis was asthmatic bronchitis with bronchopneumonia and mongolism. During the hospital stay the temperature ranged from 100° to 107° F., and an intermittent watery stool developed on the

Fig. 1.—Section of artery (× 26) and adjacent veins. Recanalization of thrombus in the artery is noted.

sixth hospital day. The patient was given penicillin and adrenal cortex therapy. On the seventh hospital day cyanosis of the right foot and the large and middle toes developed with a decrease in skin temperature and blanching below the knee. The cyanosis spread to the other toes and remained so throughout hospitalization. Both feet were cold to touch, the right being colder than the left. Pulsation of the left femoral artery was normal, and the right femoral was questionable. Oscillometric readings were absent in both thighs and ankles. The average skin temperature of the toes of the right foot was 78° F. and of the left foot varied between 80° and 83° Fahrenheit.

X-ray films revealed an anomaly of the skull and pneumonia of the right upper lobe. Serum calcium was 10 mg. per cent; phosphorous, 4.0 mg. per cent; cholesterol, 266 mg. per cent; cholesterol esters, 143 mg. per cent; thymol gel, 2; hemoglobin, 10.5 Gm.; red blood cells, 4,270,000; white blood cells, 9,600, with 68 per cent polymorphonuclear leucocytes, 30 per cent lymphocytes, and 2 per cent monocytes.

The patient expired on the ninth hospital day.

Necropsy.—The post-mortem examination revealed a mottling of the skin of the right foot There was also a mottled bluish discoloration of the left lower leg extending from the ankle to the mid-calf. The right big toe was blue-black in color and the skin was dry and friable. There was evidence of consolidation of the lower lobes of both lungs. The liver showed moderate congestion. The rest of the organs were examined and found to be grossly normal. The right iliac and femoral arteries and veins were smooth walled; the right posterior tibial and dorsalis pedis arteries showed firmly adherent thrombi which completely occluded the lumina of these vessels.

Fig. 2.—Section of arterial thrombus (× 110).

Sections of vessels from the right leg and foot (Figs. 1 and 2) showed a medium-size muscular type of artery whose lumen was filled with fibrin, with marginated clumps of erythroyctes and nucleated blood cells. The fibrin strands were poorly defined. At the periphery there were spaces partly lined by endothelium and filled with erythrocytes. Adjacent to one such vessel was a pair of intact smaller caliber veins. Other sections of arteries from this area showed similar thrombosis and recanalization. One small vein showed an unorganized thrombus. There was no inflammatory reaction in or about the walls of these vessels.

Sections of the skin of the right big toe showed poor histologic detail. There was vesiculation of the epidermis. There was marked subcutaneous edema and the capillaries were engorged. The collagenous fibers were poorly defined. No inflammatory reaction was present.

The lungs revealed changes typical of bronchopneumonia. The spleen revealed diffuse lymphoid hyperplasia and marked congestion of sinusoids. The kidneys showed congestion of renal vessels and moderate hyalin degeneration of tubular cells. Heart muscle presented moderate interstitial edema. Liver revealed slight congestion of hepatic capillaries. The rest of the organs were of average structure.

DISCUSSION

Infection and toxemia were present in both of these cases. In the first, these were of unknown origin; the second case had extensive bronchopneumonia. Severe diarrhea was present in both infants and vomiting resulting in dehydration in one.

The pathologic findings in the second case revealed a bland thrombus in the right dorsalis pedis and posterior tibial arteries without any involvement of the vessel walls. There was also thrombosis of a small vein. There was no abnormality of the heart and no evidence of any sources of emboli. The presumptive cause of thrombosis and gangrene in each of the two infants was infection.

It is well established that arterial and venous thrombosis may develop in vessels which are adjacent to a localized infection. This is explained by the fact that the infecting organisms produce local trauma to the intima of the vessel, platelets adhere to that area, thromboplastin is produced, and a clot forms. In these two cases the thrombosis may well be explained on the basis of changes in the blood which are brought about by the infection in the body. These changes include: (1) Increased viscosity of the blood produced by rise in temperature, marked sweating, vomiting, and diarrhea, all of which produce dehydration. (2) Increase in fibrinogen and changes in the electrolytes. (3) Increase in adhesiveness of the blood platelets and increased coagulability of blood plasma. Not all of these factors may be present in the same case, but any one of these may induce thrombosis.

SUMMARY

1. Two cases of gangrene of the extremities in infants, due to arterial thrombosis following systemic infection, are presented.

2. In the absence of arterial disease and a focus for embolization, it is presumed that the thromboses were caused by factors which increased the coagulability of blood.

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RECURRENT SPONTANEOUS MEDIASTINAL EMPHYSEMA SIMULATING MYOCARDIAL INFARCTION

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RECOGNITION that mediastinal emphysema may occur spontaneously, unattended by infection or trauma, has its origin in the papers of Hamman,[1] the first of which appeared in 1934. Since that time a total of forty cases have been reported in the medical literature.[2,3] Modern concepts of the pathogenesis of mediastinal emphysema have as their earliest basis the writings of Müller (1888), but it is Macklin[4,5] to whom we are indebted for clarifying and expanding our knowledge of this disease by demonstrating experimentally the manner of its occurrence, namely by dissection of air into the perivascular connective tissue of the pulmonary blood vessels to the hilus and mediastinum.

Clinically the syndrome is characterized by pain of sudden onset which is usually substernal or precordial in location. The pain varies in intensity from a vague discomfort or soreness to a severe oppression. It commonly radiates to the left shoulder and down the left arm, or up into the neck. Dyspnea, if present, is usually mild. The patient is often aware of a crackling or gurgling sensation in his chest. Fagin and Schwab[3] emphasize the absence of the picture of shock, hypotension, or appreciable tachycardia in all previously reported cases.

The first suggestive physical sign, when present, is a peculiar crunching, crackling sound (Hamman's sign) heard over the precordium during both phases of the cardiac cycle on auscultation of the chest. The area of cardiac dullness may be diminished or obliterated by a hyperresonant note on percussion. There may be a coexisting pneumothorax. Significant change in pulse, temperature, or blood pressure is uncommon. Appreciable leucocytosis, elevation of the sedimentation rate, or alteration of the electrocardiogram is absent. The roentgenogram may or may not reveal the presence of air in the mediastinum.

The following case is of interest because of the associated signs of shock and marked hypotension which were absent in all previously reported cases of this syndrome. The emphysema in this case was recurrent, and roentgenographic evidence of air in the mediastinum was present during the second episode.

REPORT OF A CASE

The patient, a 23-year-old Army Air Force pilot, was admitted to the Medical Service of the Wright Field Station Hospital on March 10, 1947, in transfer from the Dispensary at Wilmington (Ohio) Air Base, with a complaint of weakness.

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Family history revealed that the patient's father, 72 years of age, was said to have a "weak heart"; and a sister, 32 years of age, was invalided by rheumatic heart disease.

A review of past medical history revealed only scarlet fever in childhood without complications or apparent sequelae.

Present Illness.—At about 10 o'clock in the evening, three days prior to admission to the hospital, the patient became aware of the gradual onset of a sensation of "pressure" over the anterior part of the chest which he attributed to indigestion. Earlier in the evening the patient had had two glasses of beer and two mixed drinks. The sense of oppression gradually became more intense until it definitely established itself as actual pain which, as it reached its maximum severity, radiated to the left shoulder and down the left arm. The patient became dizzy and nauseated and broke out in a profuse perspiration. He experienced a profound sense of weakness and had to be carried bodily to the car which was to take him from town to the base dispensary. His companions described him as cold, clammy, and apathetic, though apparently in acute pain. He reached the dispensary at 5 A.M. and was seen by the base medical officer who found the patient in a state of shock. The skin was ashen gray, cold, and clammy. He responded feebly when spoken to. The pulse was weak and irregular, the rate 125 per minute. The blood pressure was 80/50. The heart sounds were slapping in character, and on auscultation of the precordium a crunching, crackling sound was heard during systole and diastole. This was interpreted at the time as a friction rub. The patient was presumed to have suffered an acute myocardial infarction and was given a hypodermic of ½ grain of morphine and 1/200 grain of atropine sulfate. This was repeated every four hours during the following twenty-four hours. Oxygen, by mask, was administered. The blood pressure was recorded every fifteen minutes and rose in two hours from 80/50 to 90/60. The patient could not recall how he felt in the twenty-four hour period following admission to the dispensary because he was heavily narcotized, but on the second day following the onset of his illness he was free of pain, required no analgesics, and complained only of a feeling of weakness. The following morning he was transferred to the Station Hospital, Wright Field, Ohio.

On admission to the hospital, on March 10, 1947, the patient did not appear ill. Aside from slight weakness he was asymptomatic.

Physical Examination.—Temperature on admission was 98.4°F. The pulse rate was 84 per minute and regular. The blood pressure was 100/60. The heart was of normal size and contour. The heart tones were of good quality; there were no murmurs or other adventitious sounds. The lungs were clear. The extremities revealed no calf tenderness or swelling. Homan's sign was negative bilaterally.

An electrocardiogram made on the day of admission revealed a sinus arrhythmia with a rate of 62 per minute. The P-R interval was 0.16 second. There were deep S waves in Lead I; R_2 and R_3 were tall. The RS-T segment of the limb leads was within normal limits. Chest leads CF_2, CF_4, and CF_5 were normal.

The sedimentation rate was 10 mm. in one hour (Wintrobe). Hematocrit was 48. There were 7,500 white blood cells with 62 per cent neutrophiles, 37 per cent lymphocytes, and 1 per cent eosinophiles. Urinalysis was normal. A chest x-ray (posteroanterior view) showed no abnormality.

On March 12, a second electrocardiogram was unchanged from that made on admission. The patient felt well and clamored to be up and around. Following the second electrocardiogram he was permitted to do so. On March 13, the white blood cell count was 7,900 and the sedimentation rate was 8 mm. in one hour. On March 17, a third electrocardiogram was unchanged from those taken previously. During the entire hospitalization the patient was asymptomatic. He was returned to full duty on March 18, 1947.

It was felt that the symptom complex was best explained on the basis of a spontaneous mediastinal emphysema. The nature of the illness was explained to the patient and it was suggested to him that if he should have a recurrence of chest pain, chest x-rays in the posteroanterior, lateral, and oblique views should be taken at his base medical installation.

On March 23, five days after discharge, the patient was readmitted to the hospital. He stated that since discharge he had felt well except for slight vague precordial discomfort. The evening

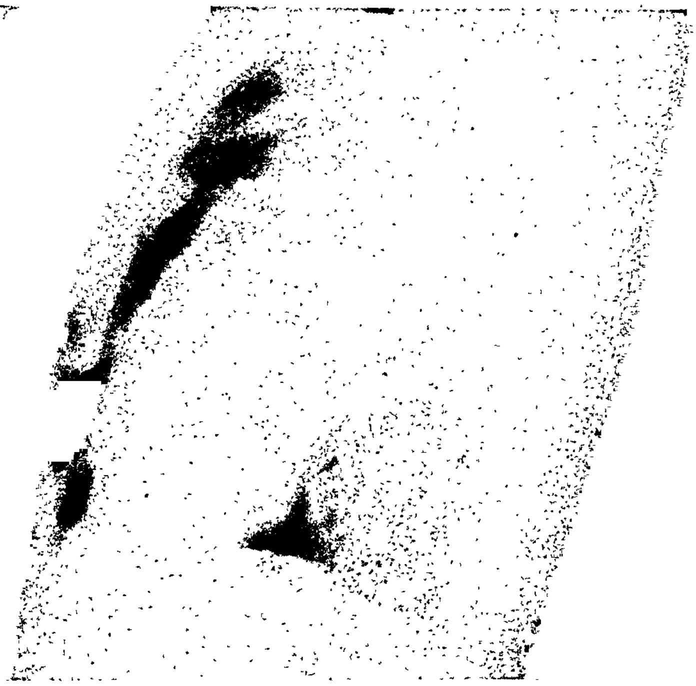

Fig. 1.—Lateral view of chest taken on day of second admission (March 23, 1947) demonstrating area of radioparency anterior to the heart. (Courtesy of Capt. G. L. Hekhuis, Chief of Radiology, Station Hospital, Wright Field.)

Fig. 2.—Lateral view of chest five days after second admission, illustrating complete return to normal. (Courtesy of Capt. G. L. Hekhuis, Chief of Radiology, Station Hospital, Wright Field.)

before readmission, while sitting quietly playing cards, the patient suddenly experienced sharp precordial pain, continuous in character. The patient stated it was like the pain of the previous episode but less severe. A distinct sense of "gurgling" in the chest was experienced which was aggravated by the prone position and relieved by an upright position. Examination by the base medical officer at that time revealed a crunching sound over the sternum and precordium like that which had been heard during the first episode. Posteroanterior, lateral, and oblique views of the chest were taken.

Examination on admission revealed an adult young man who did not appear ill. Temperature was 98.6° F; pulse, 76 per minute and regular, and blood pressure, 110/60. The area of cardiac dullness over the anterior chest wall was obliterated by a hyperresonant percussion note. A crunching sound over the sternum was audible during the entire cardiac cycle. The patient was aware of "gurgling" in the chest at the time of examination and was able to produce the noise willfully for listeners by assuming a recumbent position. The lungs were clear and the remainder of the physical examination was normal.

Sedimentation rate 4 mm. in one hour. The white blood cells were 6,400 with 49 per cent neutrophiles, 42 per cent lymphocytes, 6 per cent monocytes, and 3 per cent eosinophiles. Urinalysis was negative. An electrocardiogram revealed no change from tracings made on the previous admission. Examination of the x-ray films brought by the patient revealed, in the lateral view, an area of increased radioparency anterior to the heart extending from the mid-portion of the sternum inferiorly to just above the diaphragm. It was not visualized in the other views. X-ray films taken on admission revealed the same finding in the lateral view (Fig. 1).

On March 26, there was marked reduction in the area of radioparency previously visualized. On March 27, re-examination by x-ray showed further reduction. On March 28, there was complete disappearance of the area of increased radioparency previously seen in the lateral view films of the chest (Fig. 2). The last x-ray films were taken on April 2 and were normal in all views.

During the entire course of hospitalization the patient felt well. He had no chest pain; Hamman's sign was no longer audible after the second hospital day.

The patient was discharged on April 3, 1947, to convalescent leave. Blood pressure at the time of discharge was 126/80. The patient was last seen on May 27, 1947. Physical examination was normal. Blood pressure was 130/84. He has remained well since discharge from the hospital.

SUMMARY

1. A case of recurrent spontaneous mediastinal emphysema simulating myocardial infarction in a 23-year-old man is reported.

2. The presence of signs of shock and hypotension, not previously reported in association with this syndrome, are described.

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Abstracts and Reviews

Selected Abstracts

Goodman, M. J.: Periarteritis Nodosa With Recovery; Report of an Unusual Case Apparently Due to Sensitivity to Sulfadiazine. Ann. Int. Med. 28:181 (Jan.), 1948.

A 17-year-old white boy was admitted to the hospital after he had been treated for an acute upper respiratory infection with two courses of sulfadiazine, following which an erythematous purpuric rash, nose bleeds, fever, and generalized body aches and pains developed. These symptoms were interpreted to be a manifestation of sensitization to the drug. During his hospital stay, he developed hematuria, cylindruria, albuminuria, and a moderately severe degree of hypertension. He was extremely toxic and remained febrile for several weeks. Changes in serial electrocardiograms suggested the presence of an acute myocardial lesion. Eosinophilia in the blood smears was not a striking feature. Biopsy of the deltoid muscle established the diagnosis of periarteritis nodosa. A spontaneous recovery occurred following general supportive therapy. Examination of the patient two years after his discharge from the hospital indicated that he was in splendid health.

WENDKOS.

Rees, C. E.: A Cause for the Reestablishment of Communication Following Ligation of Patent Ductus Arteriosus. California Med. 68:35 (Jan.), 1948.

The author presents the case of a 7-year-old girl whose cardiac reserve was diminished by a patent ductus arteriosus. Ligation of the patent ductus arteriosus was carried out through a posterolateral incision, with removal of the left fourth rib. The ductus measured 1 cm. in diameter and 7 mm. in length. The thrill was completely obliterated after operation. The postoperative course was unsatisfactory from the outset because of infection. Atelectasis of the lower lobe of the left lung was observed on the roentgenogram of the chest twenty-four hours after operation and this consolidation increased within forty-eight hours. In seventy-two hours there was fluid in the left chest, and on the fifth day the amount of fluid had increased and had produced a shift of the mediastinum to the right. On the fourth postoperative day a murmur was heard over the pulmonic area, and on the ninth day this murmur had become definitely humming in character. On the tenth day the central portion of the incision was opened, old clots of blood were removed, and a tube was inserted for drainage. On the seventeenth day a portion of the ninth rib was resected and the mediastinum was explored with the finger. A large tube was inserted for continuous irrigation. Sulfadiazine, large doses of penicillin, and blood and serum transfusions failed to check the infection. The patient died on the twenty-second postoperative day.

Autopsy revealed an unexpected explanation for the re-establishment of communication between the aorta and the pulmonary artery. There was massive bilateral consolidation of both lungs and empyema on the left. The ductus lay as a necrotic cord within the ligatures. It was detached for three-quarters of its circumference from its attachment to the aorta and for one-third of its circumference from its attachment to the pulmonary artery, leaving round openings in both vessels. It was apparent that the ductus had become detached at its junctions with the main vessels and communication had become re-established between these two openings. The

detachment was probably due to tension on the wall of the ductus at the points of junction with the main vessels and necrosis of the ductus as a result of the ligation.

BELLET.

Farah, A., and Maresh, G.: Determination of the Therapeutic Irregularity and Lethal Doses of Cardiac Glycosides in the Heart-Lung Preparation of the Dog. J. Pharmacol. & Exper. Therap. 92:32 (Jan.), 1948.

The authors found that, on a molar basis, the cardiac glycosides have the following order of decreasing potency: g-strophanthin, digoxin, digitoxin, oleandrin, and lanatoside B.

The average ratios of the dose producing cardiac irregularity to therapeutic dose, and lethal dose to therapeutic dose were the same for all five glycosides studied. These findings differ from other reports in which other methods and preparations were used.

GODFREY.

Farah, A., and Maresh, G.: The Influence of Sulfhydryl Compounds on Diuresis and Renal and Cardiac Circulatory Changes Caused by Mersalyl. J. Pharmacol. & Exper. Therap. 92:73 (Jan.), 1948.

In a well-controlled series of experiments, using both anesthetized and unanesthetized animals of two species (rabbit and dog), the authors demonstrated that the diuresis caused by mersalyl was abruptly and completely inhibited by 2,3-dimercaptopropanol (BAL). The diuresis caused by intravenous infusion with sodium chloride and aminophylline was not inhibited by BAL. Cysteine hydrochloride and glutathione had no effect upon the diuresis of mersalyl even when given in very large doses.

BAL, cystein hydrochloride, and glutathione have all been found to be effective in inhibiting the cardiotoxic effects of mercurials.

To correlate the cardiotoxic inhibiting effects with the renal effects of BAL, cysteine hydrochloride, and glutathione, animals were given infusions of mersalyl and simultaneous records were made of blood pressure, electrocardiogram, and urinary output. When cardiotoxic manifestations occurred, the sulfhydryl compound was given intravenously. BAL was found to inhibit both the cardiotoxic effects and the diuretic effect of the mercurial. Cysteine hydrochloride and glutathione inhibited only the cardiotoxic action.

The characteristic diuresis caused by mersalyl is initiated by a transient reduction in urinary output. This was shown to be due to a reduction in kidney blood flow. This reduction in blood flow is completely abolished by all three of the sulfhydryl compounds (BAL, cysteine hydrochloride, and glutathione). Since only BAL inhibits the diuresis, the evidence suggests that mercurials affect more than one process in the renal excretory process.

GODFREY.

Spicknall, G. G., and Binford, C. H.: Healed Dissecting Aneurysm of the Aorta With Signs of Aortic Insufficiency. Mil. Surgeon 102:47 (Jan.), 1948.

The authors report the case of a 48-year-old white man who was admitted to the hospital complaining of shortness of breath and swelling of the ankles. He had been hospitalized previously for similar complaints. During this hospitalization hypertension and generalized arteriosclerosis were found associated with evidence of myocardial damage and myocardial insufficiency. A to-and-fro murmur was heard at the aortic area and there was evidence of a moderate grade of congestive failure. His blood pressure was 204/92. Within a few weeks after admission he became progressively more stuporous; the blood urea nitrogen rose to 46.4 mg. per cent, and the blood creatinine, to 2.4 mg. per cent. He finally became comatose, developed a uremic odor to his breath, terminal convulsions, and died.

Autopsy revealed an aortic pouch which was classified macroscopically as dissecting aneurysm of the abortive or healed type. The exact mechanism of production of the aortic incompetency in this patient is not entirely clear, although it seems probable that the lower lip of the dissecting aneurysm interfered with the closure of the aortic valve leaflets and that the cusps did not meet

in diastole because of the displacement of the commissure between the right and posterior aortic cusps. A dissecting aneurysm was not considered in the differential diagnosis in this case, and the etiology of the patient's aortic insufficiency was thought to be syphilis even though his serologic tests for syphilis were negative.

BELLET.

Hayward, G. W.: Tetraethyl Ammonium Bromide in Hypertension and Hypertensive Heart-Failure. Lancet 1:18 (Jan. 3), 1948

The present investigation was undertaken to determine whether the administration of tetra-ethyl-ammonium bromide (T.E.A.B.) would be a useful preoperative test in the selection of hypertensive patients for sympathectomy. By temporarily paralyzing the sympathetic ganglia and blocking the sympathetic vasoconstrictor impulses, tetra-ethyl-ammonium bromide might indicate whether release of vasoconstrictor tone is likely to produce a significant fall in blood pressure or not, and so help to eliminate those patients with permanent organic changes in the vessel wall who will be unsuitable for operation. In ten hypertensive patients who had a transthoracic splanchnic neurectomy performed, the blood pressure readings obtained preoperatively with tetra-ethyl-ammonium bromide and with sodium amytal have been compared with those found two weeks after the completion of the operation. Observations have also been made on the effects of administration of tetra-ethyl-ammonium bromide to patients with hypertensive heart failure.

In a preliminary group of thirty patients with essential hypertension, the comparative effects of tetra-ethyl-ammonium bromide and sodium amytal were studied. The average fall in blood pressure with tetra-ethyl-ammonium bromide was 58 mm. Hg systolic and 28 mm. Hg diastolic, as compared with 74 mm. Hg systolic and 35 mm. Hg diastolic with sodium amytal. Of the ten patients operated on (removal of the sympathetic chain and ganglia from D 6 to L 1), the operation led to fall in diastolic blood pressure of at least 20 mm. Hg in every case. The postoperative blood pressures recorded two weeks after the completion of the second stage of the operation were usually the lowest levels reached. The diastolic pressure in the preoperative test with tetra-ethyl-ammonium bromide agreed within 10 mm. Hg with the postoperative level in seven of the ten cases. With the sodium amytal test, agreement to a like degree was reached in nine of ten cases. The postoperative response of four patients to a subsequent or a similar dose of tetra-ethyl-ammonium bromide was investigated and in each case the blood pressure fell to a level lower than reached in the preoperative test.

In the present investigation there were no real toxic effects; apart from transient tingling, visual changes, and a feeling of weakness, the patients experienced no discomfort, provided they lay down for thirty minutes after the injection. In the selection of cases for operation it is important to have some preoperative test for liability of the blood pressure, the results of which agree fairly closely with the level of blood pressure found after operation. The tetra-ethyl-ammonium bromide test used in this investigation is safe, quick, and easy to carry out without discomfort to the patient. In patients with hypertensive heart failure, tetra-ethyl-ammonium bromide usually relieves orthopnea and dyspnea and causes the vital capacity, tidal air, and pulmonary ventilation per minute to increase and the venous pressure to fall. Because of its action in reducing pulmonary congestion, tetra-ethyl-ammonium bromide may be useful in the emergency treatment of paroxysmal nocturnal dyspnea or of acute pulmonary edema due to acute left ventricular failure.

BELLET.

Scheifley, C. H., and Hagedorn, A. B.: The Treatment of Subacute Bacterial Endocarditis: A Report of Forty Cases. Proc. Staff Meet. Mayo Clin. 23:1 (Jan. 7), 1948.

The records of the penicillin-treated patients which had been seen at the Clinic were reviewed by the authors. There were forty patients for whom adequate follow-up data were obtained. Thirty-one of these patients were alive and symptom free after an interval which averaged sixteen months from the time treatment was stopped. This represents a survival rate of 77.5 per cent. The patients' ages averaged 38 years and varied from 9 to 73 years. The underlying

cardiac lesion was a rheumatic valvulitis in all but two of the patients who had congenital heart lesions. The etiological agent was a green-producing streptococcus in all except three persons in whom *Streptococcus faecalis* was responsible for the infection.

For the average patient, around 300,000 units of penicillin per day were given intramuscularly in divided doses every three hours, day and night, for a period of from three to six weeks. In more recent months, this was increased to 500,000 to 1,000,000 units per day for a period of from five to seven weeks. In the case of organisms showing a high resistance to penicillin in vitro, doses as high as 10,000,000 units a day were given by continuous intravenous drip for periods of from six to eight weeks before a cure could be effected.

Of the nine patients who died, four represented definite treatment failures. In three of the nine fatalities the cause of death was unknown, but two of these patients died within a period of three weeks after the treatment was stopped and most probably represented treatment failures. In two of the nine fatalities death resulted from congestive heart failure within two months after treatment was stopped, the disease having been bacteriologically arrested. Thus, of the nine who died, six represented treatment failures while three had achieved bacteriologic arrest of their infections. A minimum of three to four weeks of continuous therapy appears necessary. The daily dose of penicillin must be adequate; a minimal daily dose, usually 500,000 to 1,000,000 units per day, is sufficient in the ordinary case. The authors feel it is safe to predict that if therapy is started early and if it is sufficiently intensive, a remarkably high percentage of recoveries will be obtained.

BELLET.

Beaumont, G. E., and Hearn, J. B.: A Case of Reversible Papilloedema Due to Heart Failure. Brit. M. J. 1:50 (Jan. 10), 1948.

A man 61 years of age was admitted to the hospital with a diagnosis of coal-gas poisoning of two days' duration. Examination revealed some justification for this diagnosis since he was in a stuporous condition, extremely dyspneic, and very cyanosed, the hands and face being a deep blue-plum color. The blood pressure was 145/95. There were marked venous engorgement, a palpable liver, and râles at the base of both lungs. It was thought that this was a case of left- and right-sided heart failure, probably secondary to long-standing emphysema, bronchitis, and asthma. X-ray examination of the chest suggested that there was some pulmonary arteriosclerosis. On routine examination of the eyes the patient was found to have pronounced papilledema of both discs. The patient was treated by venesection "cardophylin," and digitalis, and in seven days all signs of heart failure had disappeared, with the exception of some residual cyanosis of the extremities, of the ears, and of the fingers. The papilledema gradually cleared. After improvement, the patient was discharged, the blood pressure having fallen to 100/75; but two months later he relapsed and died in a second attack of cardiac failure in which the bilateral papilledema was again present.

BELLET.

Draper, A. J., Jr.: Dicumarol Poisoning. J. A. M. A. 136:171 (Jan. 17), 1948.

The author presents a case of self-medication with Dicumarol which resulted in widespread hemorrhages of serious import.

A 46-year-old graduate nurse entered the hospital complaining of pain across the middle of the back, tightness in the upper part of the abdomen, and the passage of bloody urine for two days. The patient said she had taken "eight or ten tablets" of Dicumarol for "arthritis," three weeks prior to admission. Fleeting pains throughout the limbs and trunk when the patient arose in the morning led to the diagnosis of arthritis. Physical examination revealed scattered deep purple ecchymoses some 2.0 cm. in diameter over the skin of the forearms, thighs, and flanks. Scattered petechiae were easily seen over the chest, forearms, and calves and in the mucous membrane of the mouth. The bleeding time was 5 minutes 30 seconds, coagulation time, 10 minutes plus, and prothrombin time, 1 per cent. On the day following admission, the patient was given 30 mg. of Synkayvite (a vitamin K preparation) intramuscularly, in divided doses, 60 mg. of Synkayvite intravenously twice, six hours apart, and a transfusion of 500 c.c. of fresh citrated

whole blood. By the third day the patient showed much subjective improvement. The temperature beginning the day following admission rose daily but returned to normal levels by the eighth day. The prothrombin level rose successively and reached 55 per cent on the eighth day. The coagulation time fell by the fifth day to 2 minutes 6 seconds, and the bleeding time to 1 minute 15 seconds. Blood counts had been restored to normal by the seventh day. The patient was discharged on the eighth hospital day.

BELLET.

Warren, J. V., Brannon, E. S., Weens, H. S., and Stead, E. A., Jr.: Effect of Increasing the Blood Volume and Right Atrial Pressure on the Circulation of Normal Subjects by Intravenous Infusions. Am. J. Med. 4:193 (Feb.), 1948.

The effect of increasing the blood volume by the rapid intravenous administration of 5 per cent albumin solution and physiological saline solution in normal young volunteers was studied. The observations included right atrial pressure, cardiac output, arterial pressure, plasma proteins, hemoglobin content of the blood, plasma volume, and heart size by means of teleroentgenograms.

The authors found that the increase in blood volume consistently caused a rise in atrial pressure, but the cardiac output, arterial blood pressure, and pulse rate showed no consistent change. No demonstrable change in the transverse diameter of the heart occurred with variations in atrial pressure of approximately 125 mm. of water. They conclude that increasing the blood volume and atrial pressure throws no demonstrable mechanical burden on the circulation in normal subjects and suggest that this may also be true in patients with heart failure.

The question of why fluid tends to accumulate in the lungs to such a striking degree in patients with heart failure is discussed at length.

WOODS.

Leiter, L.: Renal Diseases: Some Facts and Problems. Ann. Int. Med. 28:229 (Feb.), 1948.

Based on newer concepts of renal disease and renal physiology, the author presents a modified classification of the nephropathies. He demonstrates that the integration of pathogenesis with the altered physiology of the lesions provides a rational approach in the therapeutic management of the various types of renal disease.

He divides the organic lesions of the kidney into the following: (1) glomerulonephritis, (2) glomerulonephrosis, (3) glomerulosclerosis, (4) glomerulitis, (5) pyelonephritis, (6) vascular, (7) tubular, and (8) congenital anomalies.

The functional classification he employs is as follows: (1) vasoconstriction, (2) tubulovascular, (3) tubular (hormonal), and (4) tubular (metabolic).

Since he considers the use of the diagnosis of focal glomerulonephritis to be very dangerous from the standpoint of both treatment and prognosis, he recommends the term glomerulitis as a substitute for focal glomerulonephritis. The immunologic mechanisms which might be responsible for the development of poststreptococcal glomerulonephritis are briefly discussed. The problem of diabetic glomerulosclerosis is briefly considered and emphasis is placed on the need for recognizing that this is not an infrequent lesion. The salt retention which is a prominent feature in patients with essential hypertension is related to hormonal factors as well as to a disturbance in renal hemodynamics secondary to a generalized neurogenic vascular derangement.

The physiology of the kidney in cardiac failure is reviewed and, on the basis of such knowledge, the author shows the rationale of salt restriction in the treatment of cardiac edema.

The late renal deaths in the crush syndrome after incompatible blood transfusion reaction, in postoperative reactions, in the so-called hepatorenal syndrome, various infections and intoxications, metabolic comas, and other conditions are attributed to reflex renal vasoconstriction with ischemia of the tubular epithelium. He favors the term tubulovascular syndrome for this disturbance and considers it synonymous with the terminology of lower nephron nephrosis used by other investigators. The dividing line between the tubulovascular functional disturbances and the organic chemical nephroses or necroses of tubules is a tenuous one, and, perhaps, of only

temporal or quantitative significance in many instances. The important unifying feature has been called "functional disorganization" of the kidney. The renal tubule loses its highly selective ability to reabsorb certain elements and to discard other substances in the glomerular filtrate. Salt, nonprotein nitrogen, glucose, water, acids, bases, etc., may diffuse back completely through the disorganized tubule, especially since, on the one hand, filtration is very low and on the other hand, there is often some blockage of distal and collecting tubules by casts, pigment, debris, sulfa, and so forth. Interstitial edema of the kidney, with a tense capsule, may add further to the functional confusion. The net result is severe oliguria or anuria and uremic coma, superimposed on the patient's other troubles. The disturbance is often not recognized unless urine volume and concentration and the blood chemistry have been closely watched by the physician during his preoccupation with the patient's cardiac, peripheral vascular, pulmonary, cerebral, or skeletal situation.

In kidney disease, urinary tract obstruction should be excluded by ureteral cathetheriation. Decapsulation, the use of the artificial kidney of Koiff, or peritoneal irrigation may be required when there is urgent need for heroic treatment. He stresses the fact that the first line of attack in the treatment of medical or surgical shock after pain, anoxia, and hemorrhage have been counteracted is meticulous provision of proper conditions and materials for kidney function, leaving nothing to guesswork. The twenty-four-hour urine volume, measured at each voiding or every six hours by catheter, may be far more important than the rectal temperature or the pulse rate. Decisions as to the need for parenteral fluids should be made several times in twenty-four hours.

The paper closes with a brief discussion of the specific tubular dysfunctions resulting from various other disturbances such as diabetes insipidus, Addison's disease of the adrenals, the Cushing syndrome, renal diabetes, the Fanconi syndrome, and acidotic osteomalacia.

WENDKOS.

McKinlay, C. A.: Allergic Carditis, Pericarditis, and Pleurisy. J. Lancet 68:61 (Feb.), 1948.

The author presents a case of serum sickness associated with enlargement of the cardiac silhouette, pericarditis, and pleurisy.

A 21-year-old man was admitted to the hospital complaining of weakness, nausea and vomiting, chills, precordial pain, and dyspnea. About five hours before the onset of symptoms and seven hours before admission, he had received a prophylactic injection of tetanus antitoxin because of laceration of the right index finger. The treatment consisted of sedation with codeine and acetylsalicylic acid and intramuscular injections of penicillin, 30,000 units every three hours. The precordial ache lessened the morning following admission and the patient was discharged on the fourth hospital day with a diagnosis of serum sickness. Twenty-three days later a doctor noted for the first time a systolic murmur at the apex. Thirty-two days after onset of illness, the patient stated that the pain over the heart area had continued to trouble him. During this period of over a month he was not well, although he worked off and on and noticed that the pain was always aggravated by bending over.

The patient was readmitted to the hospital for treatment and further study. On the morning after admission a diffuse loud, to-and-fro friction rub was heard over the precordium throughout the cardiac cycle. The chest film showed diffuse cardiac enlargement. The following day, pain on breathing appeared. There also developed a pleural friction rub in the left chest and axilla with x-ray evidence of pleural effusion which had not been present twenty-four hours before. The patient improved strikingly within three days and became free from pain except for an occasional twinge in the left lower costal area. The pericardial friction rub disappeared during this period of abrupt improvement. The pleural friction likewise subsided. X-ray of the chest revealed partial clearing within five days and complete disappearance of the pleural effusion within six days of its onset; the size of the heart became normal within six days.

The authors feel that the cardiac and pleural manifestations were anaphylactic in origin.

BELLET.

Perera, G. A.: Diagnosis and Natural History of Hypertensive Vascular Disease. Am. J. Med. 4:416 (March), 1948.

The author first discusses the difficulties involved in the definition of hypertension and the impossibility of making a sharp differentiation between normotension and hypertension. The various factors which maintain blood pressure, as well as secondary regulatory mechanisms and the effect of underlying pathologic states unrelated to specific causes of hypertension, are outlined. From an analysis of the author's series of 2,000 unselected and apparently healthy men between the ages of 20 and 30 years, and from additional studies in the literature, it would appear that about 5 per cent of the adult population is afflicted with this disorder. A clear-cut family history of the disease occurs in 50 to 60 per cent of hypertensive persons.

From the records of 2,147 patients with established hypertensive vascular disease, 250 subjects were selected in whom adequate data were available from which to draw general conclusions as to the natural history of the disorder. These conclusions form the bulk of the report and emphasize that the first signs usually appear in youth and early adult life and that the average life expectancy is considerably longer than is generally assumed.

WOODS.

Scheinker, I. M.: Hypertensive Cerebral Swelling, a Characteristic Clinico-pathologic Syndrome. Ann. Int. Med. 28:630 (March), 1948.

The author analyzes the pathologic and clinical features of twelve cases of hypertensive brain disease characterized by a sudden onset and rapid progression of severe headache, drowsiness, confusion, restlessness, and delirium accompanied by signs of increased intracranial pressure, such as elevation of spinal fluid pressure and bilateral papilledema, and occasionally by convulsions, impairment of vision, and weakness of the extremities. The outstanding pathologic brain changes found in all cases consisted in a tremendous degree of cerebral swelling.

The gross findings were characterized by a considerable increase in volume of both hemispheres, flattening of the gyri, and narrowing or obliteration of the sulci; considerable enlargement of the central and subcortical white matter with consequent narrowing and compression of the cortical gray matter; loss of demarcation between white and gray matter; and decrease in size or complete obliteration of both lateral ventricles. In addition, there were disseminated ball hemorrhages in various regions of the brain tissue. Only occasionally were there massive hemorrhages. The pertinent histologic findings may be summarized thus: (1) parenchymatous changes with evidence of swelling of the nerve fibers, myelin sheaths, glia, and particularly of the obligodendroglia; (2) vascular alterations confined to the small veins and capillaries characterized (a) by congestion and stasis, and (b) by swelling and degeneration of the endothelial cells. These changes were predominant in the white matter. In addition, there were arteriolar changes characteristic of hypertensive arteriopathy. Only occasionally were there seen small focal areas of softening or glial scarring. The diffuse swelling of wide areas of cerebral tissue explains why the clinical symptomology occasionally resembles the acute manifestations of brain tumor.

Examination of the optic fundi revealed definite signs of papilledema ranging from blurring of the disc margins to pronounced swelling of from 3 to 4 diopters. The retina disclosed various stages of hypertensive retinopathy characterized by constriction and thickening of the retinal arterioles, cotton-wool exudate, recent and old hemorrhages, and venous congestion. In ten of the twelve cases the spinal fluid pressure was high, and in four cases the protein of the spinal fluid was above 130 mg. per cent. Signs and symptoms of impaired renal function were present in all cases. Repeated urinalyses disclosed albumin and casts in the majority of the cases. In only one case were there signs of hematuria. The blood urea nitrogen was in some cases moderately elevated. Only in three cases were there found levels above 100 mg. per cent. At autopsy the kidneys disclosed changes described as arteriolar nephrosclerosis in various stages of development. In but three cases were there changes characteristic of accelerated nephrosclerosis. In one instance the diagnosis of chronic glomerulonephritis was made, and in another instance the diagnosis of chronic pyelonephritis was made.

WENDKOS.

Rich, A. R.: A Hitherto Unrecognized Tendency to the Development of Widespread Pulmonary Vascular Obstruction in Patients With Congenital Pulmonary Stenosis (Tetralogy of Fallot). Bull. Johns Hopkins Hosp. 82:389 (March), 1948.

The purpose of this report is to call attention to the unrecognized tendency of patients with congenital pulmonary stenosis to develop widespread obstruction of the pulmonary vascular bed. This condition was present in 90 per cent of twenty-one consecutive cases studied at autopsy.

There are two circumstances that may be expected to favor spontaneous thrombosis in the pulmonary tree in these patients. In the first place, the anoxemia due to the inadequate pulmonary circulation results in the development of a compensatory polycythemia, often of marked degree. Polycythemia is recognized as a condition favorable to thrombosis, apparently because of the increased viscosity of the blood (see the formation of "marantic" thrombi in patients with increased viscosity of the blood due to dehydration). In addition, patients with the tetralogy of Fallot are subject to another influence, not present in patients with polycythemia vera, which can favor the development of thrombosis in the pulmonary vessels, namely, the inadequate pulmonary blood flow that results from the pulmonary stenosis. Because of this additional factor favoring thrombosis in the pulmonary vascular bed, a patient with pulmonary stenosis having the same degree of polycythemia as one with polycythemia vera should be more likely to develop thrombosis of the pulmonary vessels.

Since patients with the tetralogy of Fallot suffer from a marked deficiency in the oxygenation of the blood due to the reduced flow of blood through the lungs, the presence of widespread thrombosis of the pulmonary vessels may well add to the difficulty of oxygenation.

BELLET.

Lichtenstein, L., and Sewall, S.: Pulmonary and Cerebral Fat Embolism Following Intravenous Administration of Ether Therapeutically. J. A. M. A. 136:827 (March 13), 1948.

A fatality from fat embolism to the lungs and brain occurring during the course of intravenous administration of dilute ether solution for impending ischemic gangrene is reported. It is hypothesized by the authors that the fat emboli may have resulted from the liberation of free fat by the ether from the lipoid envelope of the erythrocytes or the emulsified fat of the plasma.

HANNO.

Ungar, H.: Diffuse Interstitial Myocarditis in a Case of Epidemic Encephalitis. Am. J. Clin. Path. 18:4 (Jan.), 1948.

The author presents the case of a 65-year-old man who was admitted to the hospital in a semistuporous condition. The illness had begun quite suddenly with a temperature of 102.2° F. which had continued since that time. The patient's condition became rapidly worse; stupor deepened and respiration became more difficult. The patient died six days following admission, on the fourteenth day of his illness.

The significant findings at necropsy were nonpurulent epidemic encephalitis and nonpurlent interstitial myocarditis. The myocardium was of a dark reddish color and, in the wall of the left ventricle (especially in its lower portion and in the septum), showed many parallel, grayish streaks. Sections from all areas contained accumulations of cells which were mainly composed of small lymphocytes and occasionally also included a limited number of polymorphonuclear leucocytes. Histologic study of the brain revealed perivascular infiltrations of a character and a distribution held to be characteristic of acute epidemic encephalitis.

The author feels that a viral myocarditis was a probable cause of the described findings. He points to the growing list of viral diseases in which myocarditis has been shown to occur and to the fact that the histologic features in such cases were similar to those observed in this case.

BELLET.

Platt, R.: Heredity in Hypertension. Quart. J. Med. 16:111 (July), 1947.

The author analyzed 116 cases of hypertension with a view to determining how many patients were without a family history of hypertension, the disease was not of the primary or essential type. The patients studied were divided into four groups: (1) those in whom the evidence of hypertension in one or both parents was strong, or if uncertain, was supported by a history of hypertensive disease in siblings of parents of patients; (2) those in whom the evidence of hypertension in either parent was lacking; (3) those in whom the evidence pointed only to a reasonable probability of hypertensive disease in one or both parents; and (4) those in whom the evidence was against hypertensive disease in either parent. In addition to the study of 116 cases, family histories were secured from seventy-one unselected patients without hypertension who were used as the control group.

This author found that approximately 76 per cent of the cases of essential hypertension gave a family history suggestive of hypertension, and in only 6.4 per cent did the family history appear to speak against hypertension. The data were not obtainable in the remainder. In the patients with secondary hypertension and in the control group the incidence of a positive family history was approximately 35 and 39 per cent, respectively.

Although it is impossible from the data available to state that essential hypertension is conveyed as a Mendelian dominant, the facts are compatible with the hypothesis that the great majority of cases in which the Mendelian rule does not seem to hold are not essential hypertension, and that careful investigation will reveal a hereditary factor in over 90 per cent of cases of essential hypertension in which the necessary data are obtainable.

BELLET.

Murray, G.: The Tetralogy of Fallot and Its Surgical Treatment. Brit. M. J. 2:905 (Dec. 6), 1948.

The author feels that the patient with the tetralogy of Fallot most suitable for surgery is the child who has survived for perhaps a year or more, has limited exercise tolerance, and has the findings characteristic of this condition. The principle of surgical treatment is to take a large branch from the aorta and anastomose it with the pulmonary artery so that more blood passes through the pulmonary circulation. In Blalock's early series the mortality rate was about 25 per cent; but according to a more recent publication it has been reduced to 17 per cent. In the author's series of sixty cases of congenital heart disease treated surgically, there were forty of Fallot's tetralogy, eleven of patent ductus arteriosus, and nine others, with an over-all mortality of 11.7 per cent and in the tetralogy cases, 7.5 per cent. All the patients received heparin postoperatively to aid in keeping the anastomosis patent. The surgical treatment of many cases of the tetralogy of Fallot is very satisfactory, bringing relief of symptoms, improvement in color, and greatly increased vigor.

BELLET.

Russek, H. I., and Zohman, B. L.: Papaverine in Cerebral Angiospasm (Vascular Encephalopathy). J. A. M. A. 136:930 (April 3), 1948.

In view of the proved effectiveness of papaverine hydrochloride as an arterial dilator in cases of arterial embolism, angina pectoris, and myocardial infarction, Russek and Zohman explored the use of this drug in the treatment of recurrent vascular encephalopathy.

A series of forty-six patients, both with and without hypertension, who presented recurring transient episodes of vascular encephalopathy were given papaverine hydrochloride by mouth in divided doses varying from 4½ to 18 grains daily. In most instances (exact figures are not given) continuous administration of the drug resulted in complete cessation of the attacks. The authors found that the concomitant use of small doses of phenobarbital (grains ¼ to ½ three times per day) appeared to reduce the amount of papaverine necessary for clinical improvement, whereas coffee and tea in excessive amounts seemed to be antagonistic to the beneficial action of the drug.

The authors state that vascular encephalopathy may occur in the absence of hypertension, and they point out that the favorable results of papaverine therapy would seem to indicate that

angiospasm may be the underlying disorder in the production of the vascular encephalopathic episode.

An additional unspecified number of patients with hypertensive headache and three patients with encephalopathy associated with acute glomerulonephritis responded favorably to oral papaverine; intravenous administration of the drug was effective in the treatment of two cases of retinal angiospasm in hypertensive patients.

It is suggested that papaverine may be of benefit in the encephalopathic episodes of eclampsia and lead poisoning.

HANNO.

Wang, S. C., and Borison, H. L.: Decussation of the Pathways in the Carotid Sinus Cardiovascular Reflex: An Example of the Principle of Convergence. Am. J. Physiol. 150:722, 1947.

In completely sympathectomized dogs in which one vagus has been sectioned, stimulation of the carotid sinus on the vagotomized side still produces bradycardia. If the opposite vagus is also excluded, no cardiac slowing ensues. Stimulation on the side of the intact vagus is less effective than stimulation of both sinuses. As the effect of change in sympathetic tone has been eliminated by sympathectomy it appears that there is a definite crossed vagal component. Decerebration experiments make it likely that the level of decussation occurs in the spinal cord and below C_2.

The bradycardia following bilateral sinus distention is invariably greater then the sum of the reduction in heart rate obtained when the two sinuses are distended separately. It is argued that this phenomenon is similar to the "fascilitation" that is seen in spinal reflexes. Sinus depressor reflexes, on the other hand, demonstrate the "occlusion" phenomenon: fall in pressure upon bilateral sinus stimulation is much less than the hypotension induced by individual stimulation of the carotid sinus.

HECHT.

Hansen, P. F. and Faber, M.: Raynaud's Syndrome Originating From Reversible Precipitation of Protein. Acta med. Scandinav. 129:81, 1947.

A 49-year-old woman with aleucemic plasma cell leucemia, running a one and one-half year course, developed as her initial symptom Raynaud attacks in the fingers and toes. Later she developed upon her face, trunk, and thigh patches of sharply circumscribed pallor which were brought on by chilling or local cold; the pallor was followed by blueness and erythema upon application of heat. These patches were painful and became progressively severe and frequent, so that preterminally the patient had to take several hot baths a day. Cavernous sinus thrombosis, retinal vein thrombosis, and loss of taste for cold food developed near the end of her course.

It was noted that her blood was difficult to smear. This proved to be due to whitish, sago-grain-sized bodies which precipitated when the blood ran at room temperature and could be seen passing along the side of containers. A "pearl necklace" effect was seen in the retinal vessels, consisting of lumps of red blood cells separated by constricted or colorless areas. The precipitation did not occur at body temperature. The substance concerned was found to be a euglobulin. Studies showed normal blood counts till near the end, and a high volume index (1.3 to 1.7), believed due to precipitation of protein with the red cells. The sedimentation rate was 2 to 6 mm. in one hour at room temperature and 145 mm. in forty-five minutes at body temperature. The serum protein total at 40° C. was 8.16, with albumin 3.96 and globulin 4.2 Gm. per cent, as opposed to 6.7 Gm. per cent total, with albumin 5.2 and globulin 1.5 at room temperature. The concentration of the euglobulin was calculated to be 2.25 Gm. per cent.

The author has seen no mention of vascular abnormalities in papers reporting abnormal protein precipitation in myelomatosis, kala azar, and other states associated with hyperglobulinemia. He believes the mechanism of the vascular abnormalities to be reversible embolism and distinguishes this process from changes in blood viscosity or vascular tone produced by cold. Ulnar nerve block did not relieve or prevent the digital attacks, which continued to be producible by cooling and reversible by heat. Plethysmography of affected fingers demonstrated

that during the "white" phase of an attack the amount of digital blood decreased markedly but pulsation remained normal, whereas in normal individuals cooling the fingers caused both decreased volume and disappearance of pulsation. This was also the consequence of cooling the proximal digital arteries while the tips of the fingers were kept warm in both the patient and the controls.

It is emphasized that though the phenomena this patient displayed were distinguishable from those of Raynaud's disease, they were sufficiently similar to be confusing. Cold-reversible embolism should be suspected in cases of Raynaud's syndrome that fail to subside spontaneously.

SAYEN.

Oehnell, R. F.: Pre-excitation and Auricular Fibrillation. Acta med. Scandinav. 129:264, 1947.

The case is presented of a 59-year-old teacher who had suffered from episodes of paroxysmal auricular fibrillation and flutter for at least eight years. Anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome) was intermittently present during the periods of both normal and abnormal auricular rhythms. The abnormal QRS complexes were usually wider during the episodes of fibrillation than when sinus rhythm was present. The absence of demonstrable P waves during the periods of circus rhythm deprives the syndrome of one important diagnostic feature, the short P-R interval. Abnormal ventricular complexes occurring at such times cannot be differentiated from aberrant responses, true bundle branch block, or ventricular extrasystoles.

HECHT.

Rasmussen, H., and Nylin, G.: The Electrocardiogram in Mitral Stenosis With Special Regard to Its Development. Acta med. Scandinav. 129:446 (No. V), 1948.

One hundred cases of mitral stenosis were studied. Most of these cases were severe, and many of the patients had had electrocardiograms made over a period of several years. Limb leads and sometimes a single chest lead were recorded. Sixty-eight per cent had auricular fibrillation.

The P waves were frequently split, most commonly in Lead II. Left axis deviation was found in 9 per cent, three patients having hypertension. Right axis deviation occurred in 26 per cent, eleven patients having right ventricular "retardation" and six, right bundle branch block. Many patients had abnormal R waves in Lead I; in only 31 per cent could this lead be considered completely normal.

The authors believe the "electrocardiographic development" consists of a progressive retardation of the right ventricular excitation which may cease at the stage of low R waves in Lead I or progress, as in 6 per cent of this group, to right bundle branch block. Since six per cent of another series of patients with left ventricular hypertrophy had left bundle branch block, it is suggested that the findings are in accord with the view that bundle branch block is most often due to enlargement of one of the ventricles.

SAYEN.

Wang, S. C., and Borison, H. L.: *An Analysis of the Carotid Sinus Cardiovascular* Reflex Mechanism. Am. J. Physiol. 150:712, 1947.

In forty dogs anesthetized with Nembutal, the carotid sinuses were exposed and cannulated. The smaller vessels leading to and from the sinus were occluded by hemostatic globulin. The sinuses were stimulated by sudden increase of intrasinus pressures. This was accomplished by unclamping the tubing of a pressure bottle filled with saline which was connected to the indwelling cannula. It was demonstrated that (1) the combined effect of vagal and sympathetic components is always greatest immediately upon stimulation, (2) the vagus appears to be responsible for most of the immediate effects, and (3) the onset of decreased sympathetic activity is slow but accounts for most of the cardiac slowing if the stimulus is prolonged. The relatively rapid disappearance of the vagal slowing (adaptation) occurs even after exclusion of vagal afferent fibers. It appears that adaptation may be related in part to "vagal escape," that is, desensitization of the heart to the vagal effects.

HECHT.

O'Neill, J. F.: The Effects of Venous Endothelium on Alterations in Blood Flow Through the Vessels in Vein Walls, and the Possible Relation to Thrombosis. Ann. Surg. 126:270 (Sept.), 1947.

The author developed a new technique of staining and mounting segments of vein wall which demonstrates with great sensitivity early changes in the endothelial cells of the vein in response to slowing of the intraluminal blood flow and to interference with the vasa venarum. In one series of experiments the femoral or jugular veins of dogs were isolated for several centimeters in order to divide the vasa venarum, and at periods of three to forty-eight hours after isolation, the veins were removed for study. The changes in the endothelial cells became more marked as the time of the period of isolation increased. In another series of experiments, metal clamps were placed around veins to narrow the lumen and hence produce partial stasis without severing the vasa venarum. The endothelial changes were less marked in severity by this technique, but in several experiments clots formed.

On the basis of his experiments, O'Neill discusses the possible relation of hypoxia and stasis to clinical venous thrombosis. Further experiments are outlined which will make use of these new techniques in the hope of arriving at a clearer understanding of the pathogenesis of venous thrombosis.

LORD.

Errata

In the paper, "The Mechanism of Irregular Sinus Rhythm in Auriculoventricular Heart Block" by Irving R. Roth, M.D., and Bruno Kisch, M.D., Am. Heart J. 36:257 (August), 1948, a correction must be made. The last part of the title of Table IV on page 266 should read, "Cycles 1 to 11 of Tracing A are illustrated in Fig. 4."

In the paper entitled "Observations on the Effects on the Lungs of Respiratory Air Flow Resistance in Dogs With Special Reference to Vagotomy" by S. Zinberg, M.D., W. G. Kubicek, Ph.D., and M. B. Visscher, M.D., Am. Heart J. 35:774 (May), 1948, a correction is necessary. In Fig. 1, page 775, the tube immersed in water should be connected to the opposite opening in the flask.

A correction is required in the paper entitled "A Simple Method of Determining Abnormalities of the Q-T Interval" by Emanuel Goldberger, M.D. Am. Heart J. 36:141 (July), 1948. In the sentence which begins on the fifth line from the end of "Discussion" on page 143, it is stated that "the normal Q-T ratio can be as large as 1.09 for men and children and 1.12 for women." The figure 1.08 should be substituted for 1.09 and the figure 1.09 should be substituted for 1.12.

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RECOMMENDATIONS OF THE RESEARCH POLICY COMMITTEE

The following recommendations of the Research Policy Committee were approved in principle by the Board of Directors and Scientific Council of the American Heart Association. These recommendations have been circularized among the membership of the Scientific Council for their suggestions. Upon final approval by the Board of Directors, these policies will govern the allocations of funds for research purposes by the American Heart Association.

The ultimate aim is to develop a continuing program of productive research within the broad field of cardiovascular disease, and it is hoped that the need for such a program over the country as a whole, rather than in a few centers only, will be considered.

I. THE TRAINING AND SUPPORT OF MEN OF OUTSTANDING ABILITY

It is the opinion of this Committee, corroborated unanimously by numerous informed individuals with whom the problem has been discussed, that the greatest contribution which could be made to cardiovascular research would be provision for continuing careers for able investigators. It is recommended, therefore, that the American Heart Association undertake to support not only investigators in training, but also, as funds are available, undertake support of the full career of proved investigators.

There are three levels at which support is obviously needed, namely, Junior Fellows, Advanced Fellows, and Career Investigators. The support for the first category is most nearly adequate. It is therefore recommended that the American Heart Association, for the near future, devote its attention to the other two groups.

1. In regard to the *Advanced Fellowships*, the following suggestions are offered:

(a) Young persons of exceptional promise should be sought for through the usual channels, and also by the obtaining of information from the Welch Fellowship Board, the Markle Foundation, the Life Insurance Fund, the Public Health Service, the National Research Council, the Guggenheim Foundation, and from similar sources.

(b) Advanced Fellows should ordinarily be appointed for five years at an initial salary of $5,000 per annum, with an annual increase of $500 up to a maximum of $7,500. Adjustments in salary in line with changes in general costs of living would be appropriate. Under special circumstances, appointments might be made for periods of less than five years.

(c) There should be a yearly grant of $500 for supplies to the institution in which these Advanced Fellows work, and applications for additional grants-in-aid would be in order for consideration by the Research Allocation Committee as hereinafter recommended.

2. From among individuals who have held Advanced Fellowships or from among others of proved outstanding ability, *Career Investigators* may be selected and appointed, subject to the following conditions:

(a) It should be the intent of the American Heart Association to provide continuing support for adequate salary and budget for the duration of a normal working career, plus reasonable provision for retirement or disability.

(b) In order to safeguard against the unusual contingency of an individual's failing to live up to the promise of his earlier career, it should be provided that the American Heart Association

may, after arranging for proper investigation by qualified experts, terminate the appointment on one year notice at any time before the incumbent has reached the age of fifty-five, providing further that the American Heart Association shall be responsible for an additional four years for meeting any adverse difference in gross income.

(c) The Career Investigator will be expected to spend at least 75 per cent of his time in research fundamentally related to problems of the cardiovascular system.

(d) In making appointments of Career Investigators, the American Heart Association should publicize the availability of positions and should invite applications from individuals, as well as applications from institutions which desire such Investigators and are willing to provide facilities. The institution to which the Investigator is attached should be approved by the American Heart Association.

II. GENERAL PRINCIPLES REGARDING GRANTS-IN-AID

1. Provisions should be made for grants for periods ranging from one to five years.
2. It should be understood that grants are not to be used to replace any obligations currently assumed by the institutions receiving the grants.
3. The desirability of a given grant should be judged primarily by the likelihood of fruitful accomplishment, as indicated by (a) the investigator; (b) the program; and (c) the soundness of the policies of the institution and its willingness to provide the necessary physical facilities, and to share financial obligations for the support of the project.
4. The advantages to be derived from developing additional intellectual centers for cardiovascular research over the country as a whole should be considered.
5. Discoveries resulting from projects supported in whole or in part by funds of the American Heart Association should be publicized through the usual channels and should not be subject to patent.

III. FLUID GRANTS

It is recommended that either now, or when more adequate funds are available, the American Heart Association undertake the policy of providing fluid research grants in the cardiovascular field for suitable institutions. It is recommended that such a fluid grant should be administered in each institution by a small committee of investigators, nominated by the administrative officer, and approved by the American Heart Association.

The availability of such fluid research funds should be publicized and institutions should be invited to make application on the basis of their needs, personnel, and facilities.

IV. COMPOSITION AND DUTIES OF THE RESEARCH ALLOCATION COMMITTEE

1. It is recommended that this Committee consist of eleven men who shall elect annually a chairman who shall appoint from among personnel of the Committee such subcommittees as may be needed.
2. It is recommended that the term of service on the Committee shall eventually be five years, but that the initial membership be staggered with three men to serve for three years, and two men to serve for one, two, four, and five years, respectively. Any man who, having been appointed for five years, has served the full period shall be permanently ineligible for reappointment. However, an individual whose initial appointment was for less than five years is subject to reappointment for five years. Thus, in the beginning, the personnel of the Committee will necessarily have changed completely at the end of nine years, and eventually the personnel will change completely over five-year periods.
3. All recommendations made by this Committee must be approved by the appropriate governing bodies of the American Heart Association before becoming effective.
4. The Committee should be selected on a wide geographic basis.
5. There should be on the Committee individuals with research experience and interest in (a) arteriosclerosis, (b) hypertension, (c) rheumatic fever, (d) peripheral vascular disease, including vascular surgery, (e) pathological physiology, (f) basic scientific disciplines, and (g) at least one individual engaged in the practice of medicine in the cardiovascular field.

6. Persons who are currently serving on other Research Allocation Committees shall be ineligible for membership on this Committee. However, either the chairman or a subcommittee should consult frequently with representatives of other agencies which are supporting research in the cardiovascular field.

V. ALTERATIONS IN RESEARCH ALLOCATION POLICY

It is believed that the Research Allocation Committee should function under these general policies until they have been altered. However, one of the functions of the Committee should be to make recommendations to the governing bodies concerning changes in allocation policy.

APPLICATIONS FOR RESEARCH GRANTS

Dr. Irvine H. Page, Chairman of the Medical Advisory Council of the American Foundation for High Blood Pressure, has announced that applications for grants for research in hypertension and arteriosclerosis may be made to the Chairman of the Allocations Committee, Dr. Harry Goldblatt, Cedars of Lebanon Hospital, Los Angeles. Other members of the Committee are Dr. Thomas Addis, San Francisco, and Dr. William Dock, Brooklyn.

AMERICAN SOCIETY FOR STUDY OF ARTERIOSCLEROSIS

The annual scientific meeting of the American Society for the Study of Arteriosclerosis will be held on Oct. 31 and Nov. 1, 1948, at the Hotel Knickerbocker in Chicago.

Newly elected officers of the Society include Dr. William B. Kountz, St. Louis, President; Dr. Irvine H. Page, Cleveland, Vice-President; and Dr. O. J. Pollak, Quincy, Mass., Secretary-Treasurer. Directors include Dr. G. Lyman Duff, Montreal; Dr. Robert A. Katz, New Orleans; Dr. E. Cowles Andrus, Baltimore; Dr. Myron Prinzmetal, Los Angeles; Dr. Louis N. Katz, Chicago; and Dr. Henry S. Simms, New York.

American Society for the Study of Arteriosclerosis

PROGRAM OF THE ANNUAL MEETING OF THE AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

TO BE HELD IN

CHICAGO, ILL., OCT. 31 AND NOV. 1, 1948

October 31, 1948

Morning

(William B. Kountz, Presiding)

9:30– 9:40 Opening Session

9:40– 9:55 **Further Studies on the Fat-Depositing Mechanism**
Henry S. Simms, Mary S. Parshley, Ruth B. Pitt, and Joan B. Fulton, Columbia University College of Physicians and Surgeons, New York, N. Y.

9:55–10:00 Discussion

10:00–10:15 **The Inhibition of Experimental Cholesterol Atherosclerosis By Alloxan Diabetes in the Rabbit**
G. Lyman Duff and Gardner C. McMillan, Department of Pathology, McGill University, Montreal, Canada.

10:15–10:20 Discussion

10:20–10:35 **Hypertension and Coronary Thrombosis**
J. C. Paterson and R. B. Holmes, Department of Pathology, University of Western Ontario, London, Canada.

10:35–10:40 Discussion

10:40–10:55 **Cerebral Vascular Changes in Arterial Hypertension**
I. Mark Scheinker, Laboratory of Neuropathology, University of Cincinnati College of Medicine, Cincinnati, Ohio.

10:55–11:00 Discussion

11:00–11:45 **Some Aspects of the Intermediary Metabolism of Cholesterol**
Konrad Bloch, University of Chicago, Chicago, Ill.

11:45–12:00 Discussion

Afternoon

(Irvine H. Page, Presiding)

2:00– 2:30 Business Session

2:30– 2:45 **The Relationship Between Dietary Composition and the Blood Cholesterol Level**
Charles F. Wilkinson, Jr., Elmira Blecha, and Ann Reimer, University of Michigan Medical School, Ann Arbor, Mich.

2:45– 2:50 Discussion

2:50– 3:05 **The Effect of a Low Fat Diet on the Spontaneously Occurring Arteriosclerosis of the Chicken**
Louis Horlick, L. N. Katz, and Jeremiah Stamler, Cardiovascular Department, Michael Reese Hospital, Chicago, Ill.

3:05– 3:10 Discussion

3:10– 3:25 **Development of Atheromatous Plaques Following Production of Intimal Atherosclerosis by Intravenous Injection of Colloidal Cholesterol Into Rabbits**
Margaret Bevans, Forrest E. Kendall, and Liese Lewis Abell, Goldwater Memorial Hospital, New York, N. Y.

3:25– 3:30 Discussion

3:30– 3:45 **The Effect of Blood Cholesterol Disorders on the Coronary Arteries and the Aorta**
Lester M. Morrison and William F. Gonzales, Los Angeles County Hospital and the Department of Internal Medicine, College of Medical Evangelists, Los Angeles, Calif.

3:45– 3:50 Discussion

3:50– 4:05 **The Clinical Diagnosis of Arteriosclerosis**
William H. Davis, Two Harbors Hospital, Two Harbors, Minn.

4:05– 4:10 Discussion

4:10– 4:25 **Clinical Significance of Blood Cholesterol**
Harry E. Ungerleider and Richard Gubner, Medical Department, Equitable Life Assurance Society of the United States, New York, N. Y.

4:25– 4:30 Discussion

4:30– 4:45 **Studies on the Cholesterol Content of the Coronary Arteries and the Blood in Acute Coronary Thrombosis**
Lester M. Morrison, Albert L. Chaney, Charles Langmade, and W. A. Johnson, Los Angeles County Hospital, Los Angeles, Calif.

4:45– 4:50 Discussion

November 1, 1948

Morning

(E. Cowles Andrus, Presiding)

9:30– 9:40 Opening Session

9:40– 9:55 **Changes in Blood Cholesterol Levels in Patients With Coronary Occlusion Following Choline Therapy**
Lester M. Morrison, Lillian Hall, and William Gonzales, Los Angeles County Hospital, Los Angeles, Calif.

9:55–10:00 Discussion

10:00–10:15 **Reactions of the Coronary Arteries of the Dog Following Injury by Allylamine**
L. L. Waters and W. B. McAllister, Department of Pathology, Yale University School of Medicine, New Haven, Conn.

10:15–10:20 Discussion

10:20–10:35 **An Evaluation of Thyroid Function in Older Individuals With Various Degrees of Arteriosclerosis**
William B. Kountz, Margaret Chieffi, and Esben Kirk, Division of Gerontology, Washington University School of Medicine and St. Louis City Infirmary Hospital, St. Louis, Mo.

10:35–10:40 Discussion

10:40–10:55 **Radiocardiography: A New Method for the Study of the Circulation**
Myron Prinzmetal, Eliot Corday, Ramon Spritzler, and H. C. Bergman, Cedars of Lebanon Hospital, Los Angeles, Calif.

10:55–11:00 Discussion

11:00–11:15 **Studies on the Relationship of Diet and Renal Insufficiency to Arterial Disease**
Russell L. Holman, Department of Pathology, Louisiana State University School of Medicine, New Orleans, La.

11:15–11:20 Discussion

11:20–11:35 **Further Studies on the Production of Arteriosclerosis in Dogs by Cholesterol and Thiouracil Feeding**
Alfred Steiner, J. D. Davidson, and Forrest E. Kendall, Goldwater Memorial Hospital, New York, N. Y.

11:35–11:40 Discussion

Afternoon

(O. J. Pollak, Presiding)

2:00– 2:15 **Sympathectomy for Arteriosclerosis Obliterans. Rationale and Results**
Alexander Blain III, Kenneth N. Campbell, and Bradley M. Harris, Department of Surgery, Alexander Blain Hospital, Detroit, and University Hospitals, Ann Arbor, Mich.

2:15– 2:20 Discussion

2:20– 2:35 **Lumbar Ganglionectomy in Peripheral Arteriosclerosis**
Leon Gerber, William S. McCune, and William Eastman, Surgical Service, George Washington University School of Medicine, and Gallinger Municipal Hospital, Washington, D. C.

2:35– 2:40 Discussion

2:40– 2:55 **Glomerular Lipoidosis in Intercapillary Glomerulosclerosis**
S. L. Wilens, S. Elster, and J. Baker, Department of Pathology, New York University College of Medicine, New York, N. Y.

2:55– 3:00 Discussion

3:00– 3:15 **The Prevention of Experimental Atherosclerosis by Choline Feedings**
Lester M. Morrison and Amerigo Rossi, Hunterian Laboratory, Department of Experimental and Internal Medicine, College of Medical Evangelists, Los Angeles, Calif.

3:15– 3:20 Discussion

3:20– 3:35 **The Absorption of Aortic Atherosclerosis by Choline Feedings**
Lester M. Morrison and Amerigo Rossi, Hunterian Laboratory, Department of Experimental and Internal Medicine, College of Medical Evangelists, Los Angeles, Calif.

3:35– 3:40 Discussion

3:40– 3:55 **Dissecting Aneurysms of the Aorta**
Jakub G. Schlichter, G. D. Amromin, and A. J. L. Solway, Pathology and Cardiovascular Departments, Michael Reese Hospital, Chicago, Ill.

3:55– 4:00 Discussion

4:00– 4:15 **New Experiments in Arteriosclerosis**
Rudolf Altschul, University of Saskatchewan, Saskatoon, Canada.

4:15– 4:20 Discussion

4:20– 4:35 **The Clinical Diagnosis of Arteriosclerosis With Particular Reference to the Use of the Roentgen Ray**
Frederic D. Zeman and Max Schenck, New York, N. Y.

4:35– 4:40 Discussion

4:40– 5:00 Closing Session

PROCEEDINGS OF THE AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS—ABSTRACTS

FURTHER STUDIES ON THE FAT-DEPOSITING MECHANISM

Henry S. Simms, Mary S. Parshley, Ruth B. Pitt, and Joan B. Fulton, New York, N. Y.

Columbia University College of Physicians and Surgeons

It has been reported previously that blood serum contains lipoid materials called "lipfanogens" that are taken up by living cells and are converted into visible fat. Serum also contains an "antilipfanogen" which prevents fat deposition in proportion to its relative concentration.

The antilipfanogen is contained in Cohn's Albumin "Fraction V." On refractionating this material at low temperature and low ionic strength, we obtain high antilipfanogen activity in the precipitate formed at pH 5.2 with 40 per cent to 50 per cent alcohol. Relatively inert material is first precipitated at pH 5.8 with 30 per cent to 40 per cent alcohol.

There is no correlation between the lipfanogen concentration in serum and its analyzable lipoid constituents (total lipoids; phospholipoids; total, free, or ester cholesterol).

On the other hand, antilipfanogen has a negative correlation with the serum cholesterol (both ester and free) and also with the phospholipoids. In nephrosis and diabetes, where the cholesterol is high, the antilipfanogen is low. In individuals with low blood cholesterol, the antilipfanogen is high.

Administration of thyroid extract appears to increase the antilipfanogen. Depancreatized dogs are being used to study the relation of antilipfanogen to blood lipoids in experimental diabetes.

THE INHIBITION OF EXPERIMENTAL CHOLESTEROL ATHEROSCLEROSIS BY ALLOXAN DIABETES IN THE RABBIT

G. Lyman Duff and Gardner C. McMillan, Montreal, Canada

Department of Pathology, McGill University

A comparison was made of the effects of cholesterol feeding in normal rabbits and in rabbits rendered persistently diabetic by means of alloxan. In both groups of animals, hypercholesterolemia of comparable degree was induced by the feeding procedure. Nevertheless, the severity of the experimental atherosclerosis of the aorta produced in the diabetic rabbits was much less than in the nondiabetic control animals. Indeed, a large proportion of the diabetic animals presented no atherosclerosis whatever. There was a similar inhibition of the deposit of lipid substance in the liver, spleen, and adrenal glands of the diabetic rabbits.

The inhibitory effect of alloxan diabetes on the development of experimental cholesterol atherosclerosis was independent of the administration of alloxan *per se.* The effect was not dependent on the sex or weight of the animal, nor upon the daily dosage of cholesterol, the form in which it was administered, nor the duration of cholesterol feeding. It was also independent of changes in body weight occuring during the course of our experiments and of the actual degree of hypercholesterolemia induced by the administration of cholesterol. In addition, there was no gross or histologic evidence of a morphologic basis for the inhibitory effect either in the aorta or in the other organs in which it was observed.

Only two factors were observed to be consistently associated with the inhibition of the expected morphologic effects of cholesterol feeding; namely, the diabetic state and a degree of visible lipemia considerably greater than that observed in the control animals.

We are quite unable to offer a specific explanation of the inhibitory effect observed in these experiments, but it would appear to depend upon some as yet undetermined factor or factors implicit in the diabetic state. The experimental data presented indicate clearly that hypercholesterolemia *per se* is not the sole factor concerned in the genesis of experimental cholesterol atherosclerosis, but that another factor or factors rendered inoperative by the diabetic state must be essential to the production of the arterial lesions.

The experimental procedures that we have employed provide a basis for the design of further experiments directed toward the elucidation of the nature of these unknown factors.

HYPERTENSION AND CORONARY THROMBOSIS

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The evidence is reviewed that the common precipitating lesion of a coronary thrombus is the liberation of thromboplastic substances from a disruptive haemorrhagic lesion in an atherosclerotic plaque of a coronary artery. Intimal haemorrhages are intrinsic lesions and are due to the rupture of newly formed capillaries that arise from the main arterial lumen. The possible causes of rupture of capillaries of this type are discussed; and it is postulated that if high blood pressure is a factor, intimal haemorrhages should be more frequent in hypertensive than in nonhypertensive individuals. Morphologic evidence is submitted to show that this is true.

CEREBRAL VASCULAR CHANGES IN ARTERIAL HYPERTENSION

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The present study aims to analyse the various types of vascular changes of the central nervous system in instances of arterial hypertension. A clinicopathologic study of 365 patients with arterial hypertension, complicated by a series of cerebral manifestations, form the material for the present study.

Attention is called to capillary changes characteristic of the *early* stage of the disease. The histologic changes typical of hypertensive arteriolopathy and their differentiation from arteriosclerosis are discussed in detail.

In addition to arteriolar changes, the following two types of venous alterations are described: (a) Reversible changes characterized by stasis congestion and distention of the vascular lumina and (b) Structural lesions of the vessel wall manifested by advanced signs of degeneration, necrosis, and an extreme degree of atrophy.

Whereas, the arteriolar changes are interpreted as significant for the disseminated foci of softening and gliosis of the nervous parenchyma, typical of chronic hypertensive encephalopathy, the alterations of the cerebral veins are regarded as responsible for the origin and pathogenesis of massive intracerebral hemorrhage so often encountered during the terminal phase of hypertensive brain disease.

SOME ASPECTS OF THE INTERMEDIARY METABOLISM OF CHOLESTEROL

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The application of modern techniques to the study of biochemical processes has led to considerable advances in our understanding of various phases of intermediary lipid metabolism. In this respect the tracer method has been of particular value by permitting the study of cholesterol synthesis in intact animals as well as in isolated tissues. Thus, the mechanism of cholesterol synthesis has been shown to involve molecules of small size as precursors, notably acetic acid. Rate studies with intact animals and experiments with isolated tissues have demonstrated the prominent role of the liver as the site of cholesterol synthesis.

Animal tissues contain a variety of compounds which, like cholesterol, possess a steroid structure but differ widely with respect to their function in metabolism. The role of cholesterol as a precursor for other steroids has been experimentally demonstrated so far for two types of compounds: the bile acids and one of the steroid hormones (progesterone).

Interest in the relation of cholesterol metabolism to cardiovascular disease arises primarily from the fact that atheromatous aortas have an abnormally high content of cholesterol. Few attempts have been made to consider this problem in the light of intermediary cholesterol metabolism. It is conceivable that such problems as cholesterol transport, cholesterol catabolism, or the regulation of the rate of cholesterol synthesis are controlling factors in pathologic lipid deposition.

THE RELATIONSHIP BETWEEN DIETARY COMPOSITION AND THE BLOOD CHOLESTEROL LEVEL

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Ninety-one individuals eating a diet of choice were studied. The cholesterol and other lipid levels of their blood were determined and from records kept over a period of time, the composition of their diet (carbohydrate, fat, protein, cholesterol, vitamins, calories, and minerals) was estimated.

Nineteen of these subjects had the metabolic disorder, essential familial hypercholesterolemia; the remainder were normal subjects. An analysis was made to determine whether a relationship between dietary composition and blood cholesterol could be established in either group.

Intake of carbohydrate, fat, protein, and cholesterol seem to have no effect on blood cholesterol; their influence on arteriosclerosis and life expectancy is discussed.

Our results, in many respects, do not agree with theories proposed in the past. However, no comparable set of data has been collected.

THE EFFECT OF A LOW FAT DIET ON THE SPONTANEOUSLY OCCURRING ARTERIOSCLEROSIS OF THE CHICKEN

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Spontaneous arteriosclerosis which resembles that seen in man has been reported to occur in 40 per cent of chickens over one year of age, and in more than 75 per cent at two years of age. We attempted to observe the effects on the frequency of occurrence and severity of the spontaneous lesions in chickens fed a diet very low in fat and liberally supplemented with vitamins.

Sixteen white leghorn cockerels were fed a diet of chick starter mash which contained 5 per cent of crude fat. Fourteen cockerels received an isocaloric mash diet with the fat content reduced to 0.3 per cent by repeated alcohol-ether extraction, and with supplements of vitamins A, B, D, and E added. The period of feeding ranged up to sixty-three weeks. Gross arteriosclerotic lesions occurred in the aortas of 63 per cent of the birds on the control diet and in 35 per cent of the birds on the low fat diet. The lesions occurred earlier and were more extensive and severe in the group receiving the normal chick starter mash. On microscopic examination fibrocellular proliferation and fat deposition were found in the intima of the aorta in both groups. The incidence of microscopic lesions was the same in both groups.

Plasma cholesterol, fatty acids, and lipid phosphorous were consistently slightly higher in the low fat group than in the control group. Complete lipid analyses of the livers and carcasses and fecal fat determinations were also done.

In this small series, restriction of fat did not prevent the development of spontaneous arterial lesions, but appeared to lessen the severity of the lesions when a parallel group on ordinary mash diet were compared.

DEVELOPMENT OF ATHEROMATOUS PLAQUES FOLLOWING PRODUCTION OF INTIMAL ATHEROSCLEROSIS BY INTRAVENOUS INJECTION OF COLLOIDAL CHOLESTEROL INTO RABBITS

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Goldwater Memorial Hospital, Welfare Island

The effect of single and multiple intravenous injections of colloidal solutions of cholesterol into rabbits was studied. It was found that 25 ml. of a solution containing 0.5 Gm. of cholesterol, stabilized with 0.1 Gm. sodium stearate introduced into a rabbit weighing 2.5 kilograms will raise the serum cholesterol level about 250 mg. per cent ten minutes after the injection. The level drops rapidly at first but values in excess of the base line level may persist for as long as one week. Repeated injections lead to serum levels comparable to those obtained when the same amount of cholesterol is fed and result in atheromatous lesions indistinguishable from those produced in feeding experiments. The intravenous technique affords an unusual opportunity to study the sequence of events which lead to the formation of atheromatous plaques. Lipid can be detected within the intima of the aorta three hours after a single injection. Gross lesions are first noted at the end of twelve daily injections.

THE EFFECT OF BLOOD CHOLESTEROL DISORDERS ON THE CORONARY ARTERIES AND THE AORTA

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An appreciable increase in the incidence of coronary arteriosclerosis and aortic atherosclerosis is described in a disease associated with chronic hypercholesterolemia; an appreciable decrease in the incidence of coronary arteriosclerosis and aortic atherosclerosis is described in a disease associated with chronic hypocholesterolemia.

It is suggested from these studies that disturbances in cholesterol metabolism may be etiologic factors in the development of coronary arteriosclerosis and aortic atherosclerosis in human subjects.

THE CLINICAL DIAGNOSIS OF ARTERIOSCLEROSIS

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It is the impression of the writer that no clearly defined and universally agreed upon criteria exist for making a clinical diagnosis of arteriosclerosis, and that little importance has been given in the past to the etiologic types and pathologic forms in making such a diagnosis.

In this paper the author has reviewed the significant literature and attempted to compile all clinically useful material from this source and from practice. Emphasis has been placed upon the means for diagnosing the condition early in its course.

The paper is presented as a survey and introductory report, with the hope that it will stimulate criticism and also further consideration and investigation of a heretofore poorly defined and often neglected phase of diagnostics.

CLINICAL SIGNIFICANCE OF BLOOD CHOLESTEROL

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Several studies have indicated that hypercholesterolemia occurs frequently in arteriosclerotic heart disease, but it has not been ascertained whether hypercholesterolemia is an etiologic factor in human arteriosclerosis or merely a concomitant of associated metabolic disorders (such as diabetes mellitus) which are responsible for degenerative vascular changes.

An analysis has been made of 104 insurance applicants with levels of blood cholesterol below 175 mg. per cent and 104 individuals with blood cholesterol above 260 mg. per cent. In addition to physical examination, blood sugar tolerance studies and electrocardiograms and teleroentgenograms were made on all subjects. Comparison is made between age, weight and body build, sugar tolerance, and the incidence of cardiovascular impairments in the group with low blood cholesterol values and the group with hypercholesterolemia. Included among cardiovascular impairment studied are abnormal blood pressure, heart murmurs, cardiac enlargement, electrocardiographic abnormalities, and roentgenologic evidence of arteriosclerosis of the aorta. No striking difference in the incidence of cardiovascular impairments between the two groups was found.

Although there is much evidence that cholesterol plays an important role in arteriosclerosis, it appears that hypercholesterolemia must be protracted over many years before vascular damage results, and that cholesterol is not the sole factor in the genesis of arteriosclerosis.

STUDIES ON THE CHOLESTEROL CONTENT OF THE CORONARY ARTERIES AND THE BLOOD IN ACUTE CORONARY THROMBOSIS

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In this study two groups of patients who had died from (a) acute coronary thrombosis and (b) non-"coronary" deaths were examined, post-mortem, to determine (1) the cholesterol content of the occluded artery and (2) the cholesterol and ester fraction of the blood. Correlations are demonstrated between (1) and (2) and their significance discussed.

CHANGES IN BLOOD CHOLESTEROL LEVELS IN PATIENTS WITH CORONARY OCCLUSION FOLLOWING CHOLINE THERAPY

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Los Angeles County Hospital

Over 100 patients have been treated with choline at regular intervals over a two-year period. The changes in blood cholesterol levels are presented and their significance discussed.

REACTIONS OF THE CORONARY ARTERIES OF THE DOG FOLLOWING INJURY BY ALLYLAMINE

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Coronary arteries of dogs have been injured by intravenous and intrapericardial injections of allylamine. The injury consists of acute necrosis of the vessel wall, reproducing many of the vascular changes seen in disease in man. Examples of the acute and chronic stages of the lesions will be shown and their pathogenesis discussed. Particulate substances, including lipids, introduced intravenously, tend to localize in the artery wall at the site of allylamine injury. Illustrations of this process will be provided.

AN EVALUATION OF THYROID FUNCTION IN OLDER INDIVIDUALS WITH VARIOUS DEGREES OF ARTERIOSCLEROSIS

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Previous work indicates that there may be a direct or indirect relationship between decreased thyroid function and the occurrence of arteriosclerosis. Oxygen consumption as is measured by the basal metabolism has been used as an index to thyroid disorders. Likewise, increased blood cholesterol levels induced in experimental animals, especially Herbivora, lead to an abnormal deposit of cholesterol in the blood vessel walls. There is some indication that in man a high cholesterol level, such as occurs in hypothyroidism and other conditions, may lead to a similar process.

Previous studies from our laboratory have demonstrated an unstableness of the rate of oxygen consumption in older individuals with degenerative disease. This finding makes it difficult to draw definite conclusions from the basal metabolic rate concerning the degree of thyroid function in older individuals who may have arteriosclerosis. Likewise, it has been demonstrated in our laboratory that the cholesterol concentration of serum shows no close correlation with the basal metabolic rate and that both men and women with calcification of the peripheral arteries may have a lower cholesterol level than patients without calcification. Since factors other than hypothyroidism are believed to influence the cholesterol level, we feel that this may not be used as an index to thyroid function. A more reliable indication would be a determination of the concentration of organic iodine in the serum, since this is regarded as an expression of the activity of the gland.

Studies, therefore, were undertaken on middle-aged and old individuals with the purpose of correlating the organic serum iodine value and the degree of arteriosclerosis. It is felt that this technique will throw more light on the rate of thyroid function in arterial degeneration. All patients investigated were subjected to a thorough study from the point of view of history, physical and laboratory findings. Repeated determinations of the basal oxygen consumption were performed, using a Sanborn apparatus, the accuracy of which was checked by alcohol combustion.

The evaluation of the three methods of study of thyroid function and the results and conclusions will be presented.

RADIOCARDIOGRAPHY: A NEW METHOD FOR THE STUDY OF THE CIRCULATION

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A radiocardiogram is a tracing which graphically records the flow of blood through the heart. It is obtained in the following manner: A lead-shielded Geiger-Mueller tube with a small window in the shield is placed over the precordium. The tube in turn is connected to an especially designed ink-writing apparatus whose pen inscribes a line on moving graph paper. A small amount of radioactive sodium (Na^{24}, 0.01 to 0.02 mg.) in 3.0 c.c. of isotonic saline is injected into the antecubital vein. As the radioactive sodium arrives in the heart, the Geiger-Mueller tube transmits the impulses to the ink-writer which records a characteristic flow through the various phases of the cardiac cycle.

In patients with cardiac enlargement without failure, typical patterns are obtained which do not differ from patients with enlargement accompanied by failure. The probable significance of this will be discussed.

Preliminary studies on congenital heart disease reveal characteristic patterns in the tetralogy of Fallot and interventricular septal defects.

Circulation time, as routinely performed, is investigated by the use of radiocardiography. The influence of such extracardiac factors as volume injected, rapidity of injection, and temperature of the extremity is illustrated.

The rate of venous flow in the upper extremity as compared with that in the lower is easily demonstrated. The latter is shown to be markedly slower, thus explaining the predilection for thrombosis in this portion of the body.

Absorption studies are carried out by injecting Na^{24} intramuscularly and placing the Geiger-Mueller tube over the site of injection. Absorption is shown to be much slower than commonly believed and almost negligible in shock. The clinical importance of this is discussed.

STUDIES ON THE RELATIONSHIP OF DIET AND RENAL INSUFFICIENCY TO ARTERIAL DISEASE

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Arterial lesions involving large elastic arteries, muscular arteries, and arterioles have been produced with regularity in dogs by feeding a specified high fat diet for two months or longer, then experimentally inducing renal insufficiency in any one of several ways. The diet can be fed indefinitely and no lesions are ever observed unless the kidneys are damaged. Any time after two months of such a diet, kidney damage is regularly followed by arterial lesions. These lesions can be prevented or retarded by vitamin E, by cholesterol, or by simply omitting the high fat supplement for four weeks or longer.

From these experimental studies, the suspicion has grown that a disturbance of fatty acid metabolism is fundamental in the genesis of arterial lesions and that the kidney plays an important role in this disturbance. Chemical injury precedes anatomical change and both are conditioned by the pattern of lipid metabolism characteristic of the species. In some species, and possibly in all, cholesterol may be primarily protective and only secondarily alterative. These studies have further suggested that arterial disease may be a matter of days rather than decades, and that the effects of age may be more cumulative than causative.

FURTHER STUDIES ON THE PRODUCTION OF ARTERIOSCLEROSIS IN DOGS BY CHOLESTEROL AND THIOURACIL FEEDING

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Goldwater Memorial Hospital, Welfare Island

It has been demonstrated (Steiner, A., and Kendall, F. E., Arch. Path. **42:** 433, 1946) that arteriosclerosis similar in distribution and morphologic characteristics to human arteriosclerosis develops in dogs following prolonged hypercholesterolemia produced by feeding 10 Gm. cholesterol daily when thyroid function is modified by thiouracil administration.

These results have been confirmed in a second series of experiments lasting twelve months upon dogs four months old at the beginning of the experiment. Extensive arteriosclerosis, including lesions in the cerebral vessels, was produced in both of the two dogs fed 10 Gm. of cholesterol and 1.0 Gm. of thiouracil each day. Minimal lesions were found in one of two dogs fed cholesterol alone and no lesions in three dogs given thiouracil alone. Studies are in progress to define more exactly the degree and duration of hypercholesterolemia required for the development of experimental arteriosclerosis in dogs.

SYMPATHECTOMY FOR ARTERIOSCLEROSIS OBLITERANS RATIONALE AND RESULTS

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Individuals suffering from the effects of obliterative arteriosclerosis of the peripheral vessels have long been thought to be beyond the reach of surgical aid as concerns measures designed to improve the circulation. This conclusion is not compatible with the experiences of several investigators who have performed lumbar sympathectomy in these patients.

The term arteriosclerosis obliterans is misleading if one presupposes that this implies inability of the smaller vessels to dilate. Despite marked organic involvement of the major vessels, the collateral and smaller vessels may be singularly uninvolved in many instances. Actually the major vessels are softer than normal rather than harder, except in areas where atheromatous plaques have become calcified. Permanent interruption of sympathetic impulses does not, insofar as we know, affect the major diseased vessels, but rather affords a more useful and extensive collateral blood supply through its effect on smaller vessels.

Sympathectomy affords a salvage in many instances so that the economic and physical liability following amputation is avoided. In our experience, the mortality following sympathectomy is less than 1.0 per cent. Even in the presence of established gangrene, arrest of the process is obtained in a worthwhile number of patients.

A few patients will not benefit from the procedure. These patients have been difficult to select and there is no uniformity of opinion among various authors regarding classification and selection of patients for the operation.

The salvage rate in eighty-three patients with advanced arteriosclerosis (Grades 3 and 4 of de Takats) subjected to sympathectomy at the University Hospital was over 70 per cent in a two-year follow-up.

Sympathectomy has proved to be a valuable prophylactic measure in patients with early symptomatic arteriosclerosis (intermittent claudication, night cramps, and cold extremities) and in patients with a single remaining lower extremity. At the Alexander Blain Hospital, patients in Groups 1 and 2 (de Takats) have been selected for operation since July, 1947. In all instances complete relief of symptoms has taken place.

More time will be necessary to evaluate the permanent effects in this series.

LUMBAR GANGLIONECTOMY IN PERIPHERAL ARTERIOSCLEROSIS

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The employment of lumbar ganglionectomy in the treatment of arteriosclerosis of the lower extremities has not enjoyed the acceptance that it has in other peripheral vascular diseases of obvious vasospastic character. The work of Flothow in 1931, using lumbar alcoholic injections began a series of studies by Robertson, Baker, Pearl, Atlas, Telford and Simmons, deTakats, Fowler, Jordan, and Risely which demonstrated the benefit of alleviating the arteriolospastic element in arteriosclerosis by interruption of the lumbar sympathetics.

Study of twenty-four patients with proved arteriosclerosis in the late stage in which minimal necrotic or gangrenous phenomena had occurred was carried out. The second and third lumbar sympathetic ganglia were removed through a muscle-splitting incision on a level with the tip of the twelfth rib.

Postoperative observation ranged from one month to forty-four months. Seventeen patients were improved, as evidenced by healing of the necrotic area after debridement or minimal amputation of a toe. The remaining eight patients were failures in which the gangrene progressed until supracondylar amputation became imperative. It was noted that the effect of sympathectomy did not disappear, but remained almost unchanged through the period of observation. Though sympathetic novocain block was employed preoperatively, it could not be depended on to indicate the expected effect of sympathectomy. The concomitant presence of diabetes in 46 per cent of the patients did not affect the results.

GLOMERULAR LIPOIDOSIS IN INTERCAPILLARY GLOMERULOSCLEROSIS

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Differential counts of the amount of lipid deposited in the glomeruli of twenty-one kidneys with intercapillary glomerulosclerosis were done on frozen sections stained with Sudan III. A statistically significantly larger amount of glomerular lipid was found than in comparable groups of twenty kidneys each of (a) arteriolar nephrosclerosis, (b) glomerulonephritis, (c) diabetes without hypertension, (d) diabetes with hypertension but without the renal lesion of intercapillary glomerulosclerosis, (e) miscellaneous renal lesions including several types of nephrosis, and (f) normal kidneys from persons of the same age span.

Not only did a larger percentage of all glomeruli from kidneys with intercapillary glomerulosclerosis contain lipid than in the control groups, but a larger number of kidneys with this lesion contained appreciable amounts of glomerular

lipid. Furthermore, the amount of glomerular lipid in intercapillary glomerulosclerosis was directly proportional to the severity of the renal lesion. This was not found to be the case in the control groups. Finally, distinctive features in the amount, form, and location of glomerular lipid deposits were noted in the group with intercapillary glomerulosclerosis.

These observations and the inferences drawn from them suggest that the deposition of fat in glomeruli is of primary importance in the development of the lesions of intercapillary glomerulosclerosis.

THE PREVENTION OF EXPERIMENTAL ATHEROSCLEROSIS BY CHOLINE FEEDINGS

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Hunterian Laboratory, Department of Experimental Medicine and Internal Medicine, College of Medical Evangelists

The oral feeding of 0.5 mg. choline chloride daily together with 0.5 Gm. cholesterol to twenty-nine three-month-old rabbits prevented atherosclerosis in 55 per cent of the animals at the expiration of the ninety-two day experimental period.

The oral feeding of 1.0 Gm. choline chloride daily together with 0.5 Gm. cholesterol to thirty-two three-month-old rabbits prevented atherosclerosis in 78 per cent at the expiration of the ninety-two day experimental period.

ABSORPTION OF AORTIC ATHEROSCLEROSIS BY CHOLINE FEEDING

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Choline caused reabsorption of aortic atherosclerosis in the majority of rabbits whose lesions had been produced by cholesterol feeding.

DISSECTING ANEURYSMS OF THE AORTA

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Fourteen cases of dissecting aneurysm of the aorta were reviewed from the morphologic and clinical aspect; two of these were on the basis of arteriosclerosis and twelve were secondary to medionecrosis of the aorta. Alterations were encountered in the vasa vasorum of nine aortas. Ischemia of the media of the aorta is implicated as the underlying primary factor in the production of medionecrosis. The various experimental, physiologic, anatomic, and congenital factors which may singly or in combination bring about medionecrosis and dissecting aneurysm are stressed. The vasa vasorum of the aorta in an instance of dissecting aneurysm were injected with radiopaque dye. The abnormal distribution of the vasa vasorum, as compared with the normal human aorta, is demonstrated.

NEW EXPERIMENTS IN ARTERIOSCLEROSIS

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A. Skeletal muscle suffers greatly in experimental cholesterol arteriosclerosis. There are two types of changes, not necessarily concomitant: (1) hyalinization, calcification, and nuclear proliferation in muscle fibers and (2) subendothelial lipoid cushions in arterioles. Guinea pigs are more gravely affected than rabbits. Denervation prior to cholesterol feeding prevents cholesterol damage. This seems to be a parallel to the findings of Pappenheimer; namely, that denervation prevents muscle damage by avitaminosis E.

B. The effect of stigmasterol on rabbits was studied to determine if it causes changes similar to cholesterol. This was tried on the grounds that stigmasterol is a phytosterol but resembles cholesterol in its formula. Moreover it does not change to any of the vitamins D. The results with feeding of stigmasterol (0.3 Gm. daily for 73 to 116 days) were negative.

C. In addition to rabbits and guinea pigs, golden hamsters also are susceptible to cholesterol arteriosclerosis. In contrast, rats are refractory. This may be explained by the fact that the latter are omnivores and readily dispose of the cholesterol. Recently, gophers were fed, for two to seven months, a milk-egg-yolk diet. None of these rodent herbivores showed cholesterol damage except cholesterol gallstones. Some foci of calcification were present, caused, perhaps, by the increased intake of vitamin D.

THE CLINICAL DIAGNOSIS OF ARTERIOSCLEROSIS WITH PARTICULAR REFERENCE TO THE USE OF THE ROENTGEN RAY

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No abstract.

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CORONARY ARTERY DISEASE IN MEN EIGHTEEN TO THIRTY-NINE YEARS OF AGE

Report of Eight Hundred Sixty-Six Cases, Four Hundred Fifty With Necropsy Examination*

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(*Continued from page 372*)

SYMPTOMATOLOGY OF THE "ACUTE ATTACK"

Symptoms of Onset.—The onset was practically always sudden and dramatic. Pain was the outstanding symptom of the "coronary attack." It was the commonest symptom both during the attack and at the onset of the attack, but it was not always the first symptom. Inasmuch as death was sudden or the patient was not seen by a physician until after death in many of the cases, the symptoms could not be ascertained in all. Altogether there were 208 of the 450 fatal cases in which the patient died so unexpectedly or in such circumstances that a history of the attack could not be obtained. Of the remaining 242 cases,

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*Joseph M. Barker, M.D., Yater Clinic, Washington, D. C., and Robert G. Angle, M.D., Bethesda, Md., aided in the collection of data and review of the literature.

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pain was present in 236 and absent in 6. In the group of 400 patients who survived an attack of acute myocardial infarction, pain was the most noteworthy symptom in 396 cases. Therefore, of 642 cases in which a history could be elicited, pain was present in 632 patients (98 per cent). It was the primary or first symptom in 575 patients (90 per cent) but ensued rapidly in the other fifty-seven.

The primary symptoms of the onset of the attack are listed in Table XX. There it will be noted that manifestations of shock, such as weakness, sweating, pallor, and small, rapid pulse, were the next most common symptoms (17 per cent), and that these symptoms occurred naturally much more often in the group of fatal cases than in those patients who survived (37 per cent as compared with 5 per cent). Dyspnea occurred at the onset in 9 per cent of the patients, and nausea, vomiting, or both were present in 7 per cent. Other symptoms worthy of note were much less common.

Subsequent Symptoms.—As the attack progressed, symptoms other than the initial one rapidly ensued, but on the whole, the list is similar; in fact, several symptoms occurred almost simultaneously from the start in many cases. This accounts for the fact that in Table XX the percentage figures aggregate more than 100. For instance, among the fatal cases manifestations of shock were noted 313 times*; dyspnea and/or pulmonary congestion (râles) and/or cough in 159

TABLE XX. PRIMARY SYMPTOMS AT ONSET OF ACUTE ATTACK IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE

SYMPTOMS	FATAL CASES*		SURVIVORS		TOTAL	
	NO.	%†	NO.	%†	NO.	%†
Pain	236	97.5	339	84.8	575	89.6
Manifestation of collapse or shock	90	37.2	19	4.8	109	17.0
Dyspnea	20	8.3	37	9.3	57	8.9
Nausea, vomiting, or both	25	10.3	17	4.3	42	6.5
Indigestion	13	5.4	3	0.8	16	2.5
Syncope	4	1.7	7	1.8	11	1.7
Dizziness	6	2.5	4	1.0	10	1.6
Palpitation of heart	1	0.4	4	1.0	5	0.8
Congestive failure	5	2.1	0	0.0	5	0.8
Convulsions	4	1.7	0	0.0	4	0.6
Nervousness or psychic depression	2	0.8	2	0.5	4	0.6
Diarrhea	3	1.2	0	0.0	3	0.5
Hemiplegia	3	1.2	0	0.0	3	0.5
Choking	0	0.0	2	0.5	2	0.3
Delirium	1	0.4	0	0.0	1	0.2
Anorexia	1	0.4	0	0.0	1	0.2
Numbness in arms			1	0.3	1	0.2
Total patients with symptoms	242		400		642	

*Of the 450 patients, 208 either died too soon to be questioned or their history was unknown.

†Percentages are based on total number of patients with symptoms. This and the fact that there may have been more than one primary symptom account for the fact that the percentage figures aggregate more than 100.

*This figure represents the sum of symptoms considered manifestations of shock, namely, sweating, weakness, collapse, pallor, cyanosis, and a sensation of heat.

patients; nausea, vomiting, or both in ninety-nine; restlessness, nervousness, or apprehension in twenty-seven; unconsciousness in twenty-seven, convulsions in twenty-five, "indigestion" in thirteen, congestive failure in ten, and diarrhea (a noteworthy symptom) in eight patients. Among the survivors, individual symptoms of shock were noted 436 times, but physicians considered only thirty patients to be in "shock." In this group also there were dyspnea and/or pulmonary congestion (râles) and/or cough in 216 patients; nausea, vomiting, or both in 134; restlessness, nervousness, or apprehension in ninety-two; unconsciousness in forty-five, convulsions in none, "indigestion" in thirty-three, congestive failure in none, and diarrhea in seven. Other symptoms, as shown in Table XXI, were choking, anorexia, constipation, dizziness, mental dullness, chills, headache, palpitation, numbness of one or both arms, thirst, desire to

TABLE XXI. SUMMARY OF MAIN SYMPTOMS OF THE "ATTACK"* IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE

SYMPTOMS		FATAL CASES		SURVIVORS		TOTAL	
		NO.	%	NO.	%	NO.	%
Pain		236	97.5	396	99.0	632	98.4
Weakness	Symptoms of Shock	89	36.8	123	30.8	212	33.0
Collapse	Symptoms of Shock	152	62.8	41	10.3	193	30.1
Sweating	Symptoms of Shock	13	5.4	148	37.0	161	25.1
Cyanosis	Symptoms of Shock	45	18.6	46	11.5	91	14.2
Pallor	Symptoms of Shock	11	4.5	58	14.5	69	10.7
Heat†	Symptoms of Shock	3	1.2	20	5.0	23	3.6
Dyspnea, cough, râles		159	65.7	216‡	54.0	375	58.4
Nausea, vomiting, or both		99	40.9	134	33.5	233	36.3
Nervous manifestations§		27	11.2	92	23.0	119	18.5
Unconsciousness		27	11.2	45	11.3	72	11.2
Numbness‖		10	4.1	59	14.8	69	10.7
Indigestion¶		13	5.4	33	8.3	46	7.2
Dizziness		10	4.1	29	7.3	39	6.1
Palpitation		1	0.4	33	8.3	34	5.3
Convulsions		25	10.3	0	0.0	25	3.9
Choking or gagging		9	3.7	16	4.0	25	3.9
Anorexia		1	0.4	16	4.0	17	2.6
Headache		0	0.0	15	3.8	15	2.3
Diarrhea		8	3.3	6	1.5	14	2.2
Congestive failure		10	4.1	0	0.0	10	1.6
Hemiplegia		3	1.2	2	0.5	5	0.8
Chills		4	1.7	0	0.0	4	0.6
Constipation		1	0.4	3	0.8	4	0.6
Thirst		2	0.8	0	0.0	2	0.3
Tympanites		2	0.8	0	0.0	2	0.3
Delirium		1	0.4	0	0.0	1	0.2
Desire to defecate		1	0.4	0	0.0	1	0.2

*By "attack" is meant the acute manifestations of onset of coronary insufficiency, with or without acute coronary artery occlusion.

†By "heat" is meant a subjective sensation of body warmth.

‡This figure includes twenty-two cases of orthopnea and twenty-one cases with cough, five with bloody sputum.

§"Nervous manifestations" includes restlessness, nervousness, anxiety, apprehension, fear of death, psychic depression, and mental dullness.

‖"Numbness" refers to a feeling of numbness in shoulders, arms, hands, fingers, and legs.

¶"Indigestion" usually means a sensation of fullness or of a lump in the epigastrium without actual pain.

defecate, swelling of the abdomen, and hemiplegia. The difference between the two groups may be accounted for on the basis of duration and severity, the men surviving naturally having milder manifestations on the whole.

The most difficult symptoms to tabulate and evaluate were those which might be attributed to shock. In the group of survivors, 148 had sweating; 123, weakness or tiredness; fifty-eight, pallor; forty-six, cyanosis; forty-one, collapse; and twenty, a subjective sensation of heat; but in only thirty were the combinations such that the physician designated the state of the patient as one of "shock." The inadequacy of observations and records of many different physicians make these figures inaccurate, but still they indicate a trend.

Pains.—The various locations in which the prominent symptom of pain in the fatal group occurred are shown in Table XXII. The division of anterior thoracic pain into precordial and substernal is admittedly inaccurate. Many of the instances of precordial pain were probably mainly substernal. Because of the radiation from the primary site, usually the anterior thoracic region, there were two or more sites in fifty-two cases. Pain did not radiate in 184 patients, a feature worthy of note. In the eight patients in whom it occurred in the back it had usually radiated from the front. Anterior myocardial infarcts were found in five of these patients.

TABLE XXII. LOCATION OF PAIN IN FATAL CASES OF CORONARY DISEASE IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE

LOCATION	NUMBER	
Thoracic (anterior)		178
Location not given*	77	
Precordial*	59	
Substernal	42	
Thoracic (posterior)		8
Abdominal		55
Location not given	18	
Epigastric	28	
"Stomach"	9	
Left shoulder and arm		23
Both shoulders and arms		10
Wrists		2
Fingers		1
Neck		5
Head		1
Calves of legs		1
Bones		1

*Many of these were probably substernal.

Descriptions of the character, severity, radiation, and duration of pain were naturally sketchy because so many of the patients were very ill. In four patients in whom the pain was adequately described, it was mild; in seventeen, moderate; and in eighty-four, severe. It was variously described as oppressive (thirteen), constricting (seven), numbing (four), burning (three), sharp (two), aching (two), tearing (one), dull (one), rheumatic (one), and as a soreness (one). In the cases of sudden death (minutes to hours) the duration of the pain was not

stated, but in twenty-eight cases in which the men lived longer than twenty-four hours the duration of the initial attack was given as follows: 1 to 5 minutes in three, 6 to 15 minutes in four, 16 to 30 minutes in one, 30 minutes to 4 hours in twelve, 5 to 12 hours in three, 1 day in one, 2 days in one, and 3 days in three.

Statements made by the men concerning factors which induced pain are not reliable, since in so many of the cases the pain "just developed." However, seventeen said it was induced by exertion; three, by rest; and five, by eating. Many of the men were given injections of morphine, but there are no accurate figures as to its effectiveness. The pain was relieved by rest in four cases, by drinking water in two, spontaneously in two, and by the use of nitroglycerin in one.

More exact were the data concerning pain in the 400 cases of the survivors. Pain was the outstanding symptom in 396 (99 per cent) of these. It occurred as the initial symptom in 339 and developed soon after the onset of the "attack" in fifty-seven more. In 220 patients the pain was described as constricting in fifty-three, oppressive in fifty, pressing in forty-eight, as a numbness in forty-two, sharp in thirty-seven, viselike in twenty-five, aching in twenty-two, knifelike in twenty, as a tightness in eighteen, crushing in thirteen, squeezing in thirteen, stabbing in twelve, burning in twelve, heavy in nine, sticking in eight, as a soreness in seven, cramplike in six, tearing in six, gripping in five, compressing in four, agonizing in four, as a sensation of a lump in four, boring in three, cutting in three, as a pounding in three, as smothering in three, as choking in two, and hammerlike, shocking, shooting, stinging, and throbbing in one each. In eighteen cases the pain was not described. These types of pain may be grouped as follows: (a) oppressive, pressing, crushing, heavy, compressing, smothering, and choking in 129 patients; (b) constricting, viselike, as a tightness, squeezing, and gripping in 114; (c) sharp, knifelike, stabbing, sticking, cramplike, tearing, cutting, shooting, and stinging in seventy-four; (d) aching, burning, as a soreness, and boring in forty-four; (e) numbness in forty-two; (f) pounding, hammerlike, and throbbing in five; (g) agonizing and shocking in five; and (h) as a lump in four.

So far as could be judged from the description, the pain was severe in 305 of the survivors, moderate in fifty-four, and mild in twenty-four. Of the remaining seventeen survivors, there was no pain in four and in thirteen the data were too meager to permit classification.

A striking feature of the pain in forty-one (approximately 10 per cent) of the survivors was exacerbation of the pain on deep breathing. In none of these patients was there evidence of pericarditis or pleurisy on physical or roentgenographic examination.

The substernal and left anterior thoracic areas were the most common sites of pain among the survivors. Pain was described as definitely substernal in 192 cases, as precordial in ninety-five cases, and as left anterior thoracic in thirty. Other locations were the epigastric region (twenty), the abdomen (four), the neck and throat (three), the mouth, teeth, and jaws (two), the legs only (two), and both arms, below the left scapula, the back between the shoulders, the left axilla, the left side of the chest posteriorly, the left elbow, the left shoulder,

the right shoulder, and the head (one, each). Forty patients stated that they had pain in the chest but did not localize it.

Among the 396 survivors who gave a history of pain, it was stated to have radiated to various parts of the body in 272 cases (69 per cent), proportionately many more than in the acutely fatal group. The patients described the radiation very accurately. In many cases the pain radiated to more than one part of the body. The various areas of radiation were as follows: left arm (ninety-nine), both arms (eighty-one), left shoulder (sixty-eight), neck (thirty-eight), shoulders (thirty-five), back (thirty-five), another part of the chest (twenty-two), to the precordium from the sternal region (twenty-two), mouth and jaws (twenty-one), to the sternal region from the precordium (fourteen), to the left side of the chest from the sternal region (eleven), right arm (ten), fingers (nine), wrists (eight), head and face (seven), abdomen (seven), elbows (six), right shoulder (six), left shoulder (six), left axilla (six), fingers of the left hand (six), right side of chest (five), left elbow (four), left hand (four), hands (three), legs (three), left wrist (two), axillae (two), right axilla (two), palate (two), nipple (one), and all extremities (one).

Among the survivors, the duration of pain during the acute attack was from a few seconds in one case to twenty-one days in another. The pain was considered to be continuous during the acute phase in 314 patients and intermittent in eighty-two. There was no apparent relationship between the duration of the pain and the subsequent clinical course. Ten seconds was recorded as the shortest duration of pain, and the patient in whom this duration was recorded experienced an otherwise typical clinical course with classical electrocardiographic changes, fever, leucocytosis, and increased sedimentation rate (see Case 71). On the other hand, the patient who had continuous substernal pain for twenty-one days described it as severe for forty-eight hours and then as a constant dull ache for the next nineteen days. In many instances the duration of pain was directly affected by the medication given, such as morphine or other analgesic drugs. In the group of 314 patients with continuous pain, twenty-five (8 per cent) had pain for less than one hour, ninety-five (30 per cent) for one to four hours, 136 (43 per cent) for four to twenty-four hours, thirty-one (10 per cent) for twenty-four to forty-eight hours, and twenty-seven (9 per cent) for more than forty-eight hours. In the group of eighty-two patients with intermittent pain, the pain lasted from a matter of seconds to five hours and recurred one or more times during the "acute coronary attack."

Clinical Course of the Fifty-four Patients Hospitalized for Twenty-four Hours or More Before Death.—Fifty-four of the soldiers who died were in a hospital twenty-four hours or more, and many of them were examined adequately. In six the course of the disease following the initial attack was asymptomatic and death occurred suddenly (Table XXIII). In fourteen cases the patients were improving and died unexpectedly. Recurrent pain of anginal type occurred in forty-five patients, with the number of attacks as listed in Table XXIII. Pain was present terminally in twenty-two patients. Congestive failure ensued in thirteen patients; this figure includes five patients in whom it had been present

for one to seven months before final hospitalization. Embolization occurred in five patients and convulsions, in six.

The course was typical of myocardial infarction in thirty-one patients, but in two of these no infarction was found; in one there was an organizing thrombus in the left anterior descending artery; in the other, sclerotic occlusion of the left anterior descending and right circumflex arteries. In the first of these, electrocardiograms showed typical anterior myocardial infarction; in the second, atypical anterior myocardial infarction.

TABLE XXIII. SYMPTOMS OF COURSE IN FIFTY-FOUR FATAL CASES—PATIENTS HOSPITALIZED BECAUSE OF CORONARY DISEASE

HOSPITAL COURSE	NUMBER*	
Asymptomatic with unexpected death		6
Improving but death unexpected		14
Recurrent pain of anginal type		46
1 attack	14	
2 attacks	7	
3 attacks	4	
4 attacks	3	
Numerous attacks	9	
Continuous	9	
Pain present terminally		22
Dyspnea		15
Congestive failure†		13
Pulmonary congestion		11
Convulsions		6
Shock		6
Embolization		5
Nausea and vomiting		4

*The total of this column of 148 means that some of the symptoms were combined in individual cases.
†Five had congestive failure prior to hospitalization; eight developed it during hospitalization.

The cardiac signs in these cases were not unusual. There were no abnormal findings in twenty-nine patients. The heart was enlarged in six; the heart sounds were distant in seven; a systolic murmur was heard in six, There were premature beats in five patients, tachycardia in five, and gallop rhythm in five. A pericardial friction rub was heard in only one patient. An aortic diastolic murmur was present in one patient. This was a case of syphilitic aortitis with complete occlusion of the orifice of the right coronary artery and almost complete occlusion of that of the left coronary artery. Other physical signs were those to be expected, such as pulmonary congestion, cyanosis, dyspnea, and edema.

The blood pressures were normal or low in all but twelve patients, in eight of whom the pressures were slightly elevated, in one, moderately elevated, and in three, high (200/120 to 224/129).

The temperature was above normal in thirty-two cases and remained elevated for a longer time than in the patients who recovered. However, the number of cases is not large enough to warrant emphasis of this point. In twenty-eight patients the temperature was less than 103°F. at the highest, ranging in most from 99 to 102° Fahrenheit. In three patients the highest reading was

from 103 to 105°F., and in one patient the temperature rose terminally to 108° Fahrenheit.

The sedimentation rate in this group of cases was of very little help. Fifteen patients had a normal rate; four, a slightly elevated rate; three, a moderately elevated rate; and four, a greatly increased rate. In the other patients the rate was not recorded.

Roentgenograms of the chest were made in most cases. The heart shadow was found to be enlarged in nineteen patients; evidence of pulmonary congestion or edema was noted in nine, and infarcts of the lungs were stated to be present in three patients. Pleural effusion was evidenced in two patients, thickened pleura in one, atypical pneumonia in one, and "pneumonitis" in one patient.

Electrocardiograms.—Electrocardiograms were made in only forty-nine of the entire series of 450 fatal cases, ten in cases in which death occurred within twenty-four hours and thirty-nine in cases in which the duration was more than twenty-four hours. The number of electrocardiograms made in individual cases varied from one to eleven. Table XXIV shows the time elapsing between the last electrocardiogram and death, the electrocardiographic findings or the interpretation of them, and the pathologic findings. This table speaks for itself and

TABLE XXIV. ELECTROCARDIOGRAPHIC DATA IN RELATION TO PATHOLOGIC FINDINGS IN FORTY-NINE PATIENTS WHO DIED OF CORONARY DISEASE

TIME MADE BEFORE DEATH	ELECTROCARDIOGRAPHIC DATA	PATHOLOGIC FINDINGS
	Cases in Which Death Occurred Within Twenty-four Hours	
Just before death	S-T_2 and S-T_3 depressed	Infarct 0.2 by 5 cm. in posterior wall of left ventricle involving septum with thrombosis of left circumflex artery
Day of death	Normal	Infarct 1.5 cm. in diameter in anterior one-third of septum with thrombosis of right coronary and left circumflex arteries
4 months	Not available	No infarction; sclerotic occlusion of left anterior descending artery with thrombosis
2 months	Inverted T in IV F	Infarct of left ventricle with sclerotic occlusion of left anterior descending, right circumflex, and left circumflex anterior arteries
8 months	QRS N-shaped; late inversion of T in CF_3, slight late inversion of T in CF_3	No infarction; sclerotic occlusion of left anterior descending artery with thrombosis
2 months	S-T_2 and S-T_3 inverted; Q_3 present	No infarction; sclerotic occlusion of all coronary arteries
1 month	Normal	No infarction; thrombus in left anterior descending artery
1 day	Atypical infarction	No infarction; sclerotic occlusion of left anterior descending and left circumflex arteries
Not recorded	4:1 heart block	Infarct 8 by 4 cm. in wall of left ventricle with thrombosis of left anterior descending artery
2 days	Normal	No infarction; sclerotic occlusion of right circumflex artery

TABLE XXIV. ELECTROCARDIOGRAPHIC DATA IN RELATION TO PATHOLOGIC FINDINGS IN FORTY-NINE PATIENTS WHO DIED OF CORONARY DISEASE—(CONTINUED)

TIME MADE BEFORE DEATH	ELECTROCARDIOGRAPHIC DATA	PATHOLOGIC FINDINGS
Cases in Which Patients Lived More Than Twenty-four Hours		
Days	Typical anterior infarction	Infarct of half of left ventricle and septum 5 by 3 cm. with sclerotic and thrombotic occlusion of left anterior descending artery
2 months	Typical anterior infarction	Infarct, massive, of left ventricle and septum with thrombus in left anterior descending artery
2 days	Typical anterior infarction	Infarct in anterior wall of left ventricle and septum with thrombus in left anterior descending artery and sclerotic occlusion of left circumflex artery
1 day	Typical anterior infarction	Infarct in apex of left ventricle anterior with thrombus in left anterior descending artery
20 days	Typical anterior infarction; right bundle branch block	No infarction; organizing thrombus in left anterior descending artery
2 months	Typical anterior infarction	Infarct 3 by 1 by 0.8 cm. in anterior portion of left ventricle and septum with thrombus in left anterior descending artery
Day of death	Typical anterior infarction	Infarct 2 cm. in diameter in left ventricle with thrombus in left anterior descending artery
21 days	Typical anterior infarction	Infarct 3 cm. in diameter in apex of left ventricle and septum with thrombus in left anterior descending artery
2½ months	Typical anterior infarction	Infarct in interventricular septum with sclerotic and thrombotic occlusion of left anterior descending artery
11 months	Typical anterior infarction	No infarction; simple narrowing of coronary arteries
Not recorded	Typical anterior infarction	Infarct of left ventricle and septum with thrombus in left anterior descending artery
2 days	Typical anterior infarction	Infarct 7.5 by 5.4 cm. in apex of left ventricle and septum with thrombus in left anterior descending artery
7 weeks	Typical anterior infarction	Infarct in apex of left ventricle; practically complete sclerotic occlusion of proximal third of all cornary arteries.
Day of death	Typical posterior infarction	Several infarcts left ventricle and right ventricle with thrombosis of right circumflex artery
2 months	Typical posterior infarction	No infarction; thrombotic occlusion of left anterior descending artery
6 days	Typical posterior infarction	Infarct 3 by 3 cm. in posterior wall of left ventricle and septum with thrombosis of right circumflex and left anterior descending arteries
1½ months	Atypical anterior infarction	Infarct in anterior wall of left ventricle with organized thrombus in left anterior descending artery
4 days	Atypical anterior infarction	No infarction; sclerotic occlusion of left anterior descending and right circumflex arteries
19 days	Atypical posterior infarction	No infarction; thrombosis of left anterior descending artery

TABLE XXIV. ELECTROCARDIOGRAPHIC DATA IN RELATION TO PATHOLOGIC FINDINGS IN FORTY-NINE PATIENTS WHO DIED OF CORONARY DISEASE—(CONTINUED)

TIME MADE	ELECTROCARDIOGRAPHIC DATA	PATHOLOGIC FINDINGS
1½ months	Anterior and posterior infarction	Infarct 2 by 4 cm. in anterior wall of left ventricle with sclerotic occlusion of left circumflex and right circumflex arteries
Not recorded	Anterior and posterior infarctions	Infarct 4 by 4 cm. in apex of left ventricle with thrombosis of left anterior descending artery
1 day	Anterior and posterior infarctions	Infarcts in apex of left ventricle, posterior basal portion of left ventricle, and right ventricle, with thrombosis of left anterior descending and right circumflex arteries
5½ months	Atypical infarction; defective intraventricular conduction	No infarction; simple narrowing of coronary arteries
1 day	Atypical infarction; right bundle branch block; auricular flutter	No infarction; sclerotic occlusion of left anterior descending artery
4 days	Myocardial damage	Infarct in anterior wall of left ventricle with thrombosis of left anterior descending artery
2 days	Myocardial damage	Infarct 3 cm. in diameter in anterior wall of left ventricle with thrombosis of left anterior descending artery
2½ months	Myocardial damage	Infarcts in left and right ventricles with sclerotic occlusion of left anterior descending and right circumflex arteries
2 days	Myocardial damage	Infarcts in posterior wall of left ventricle and septum with simple narrowing of coronary arteries
1½ months	Myocardial damage	No infarction; sclerotic occlusion of left anterior descending artery
2 days	Myocardial damage	No infarction; thrombosis of left anterior descending artery
23 days	Myocardial damage	No infarction; sclerotic occlusion of left anterior descending artery
13 days	Myocardial damage	No infarction; sclerotic occlusion of left anterior descending artery
8 days	Myocardial damage	No infarction; sclerotic occlusion of left circumflex artery
2 months	Myocardial damage	No infarction; sclerotic occlusion of left anterior descending and right circumflex arteries with fresh thrombosis of the former
4 days	Myocardial damage	Infarct in posterior wall of left ventricle and septum with thrombosis of all three major arteries
10 days	Myocardial damage	Infarct in wall of left ventricle with sclerotic occlusion of left anterior descending and right circumflex arteries
Not recorded	Myocardial damage	Infarct 4 by 6 cm. in anterior wall of left ventricle with sclerotic occlusion of left anterior descending and left circumflex arteries
3 months	Myocardial damage	Old massive infarct in anterior wall of left ventricle and septum with old thrombotic occlusion of left anterior descending artery
3 days	Normal	No infarction; thrombosis of left anterior descending artery

shows the number of discrepancies, many of which might have been obviated had a greater number of precordial or V leads been used. It is notable that there were four normal electrocardiograms, made, respectively, one month, three days, and two days before death, and on the day of death. The first three were recorded in cases without infarctions but with complete occlusion of major coronary arteries, the fourth in a case with infarction and thrombosis of the right circumflex and left anterior descending arteries.

Clinical Diagnosis.—The clinical diagnosis was correct in 116 of the 450 fatal cases. The diagnosis was considered correct for practical purposes if coronary artery disease or any phase of it was given. The diagnoses were correct in eighty-three of the 375 cases in which death occurred within twenty-four hours and in thirty-three of the seventy-five cases in which the patient lived more than twenty-four hours. It must be noted, however, that in 247 of the cases of sudden death the patient expired before a medical officer saw him. Thus, there were 203 opportunities to make a diagnosis on living patients. The diagnostic accuracy is, therefore, 58 per cent.

Physical Examination of the Survivors.—The records of physical examinations made during or shortly after the acute attack were available in 388 of the 400 cases. In 185 (48 per cent) of the cases, an abnormality of the pulse was noted. The pulse rate was rapid (above 100 per minute) in ninety-one, slow (below 60 per minute) in sixty-four, and considered to be of poor quality or feeble in thirty patients. Arrhythmias were present in sixty-two additional patients (see cardiac findings). In all instances the pulse was considered to be normal in quality and rhythm after a period of hospitalization.

The cardiac findings were of considerable interest because of the large group of patients with entirely normal physical findings. In 231 (60 per cent) of the 388 cases, the physical examinations of the heart were recorded as entirely normal. The most frequently observed cardiac abnormality, that of poor heart sounds, described by various examiners as distant, feeble, weak, faint, and muffled, was found in seventy-two patients. Cardiac arrhythmias were noted in sixty-two patients; premature ventricular contractions were heard fifty-seven times, paroxysmal auricular tachycardia and auricular fibrillation, two times each, and auricular flutter, once. These arrhythmias were transient and ceased within twenty-four hours after hospitalization in every instance. Murmurs were heard in thirty-five patients during the initial examination; in thirty-three the murmurs were systolic and in two they were thought to be diastolic; in thirty-two patients these murmurs were heard over the mitral area, and in three, systolic murmurs were heard at the base. The murmurs were transient, none were considered characteristic of any definite valvular lesion, and all had disappeared before the patients were discharged from the Army hospitals. Gallop rhythms were heard in twenty patients during the first examinations; but no exact descriptions of the timing were available, and in only three instances did the gallop rhythm persist.

Several other abnormal cardiac findings were observed and are worthy of mention. Cardiac enlargement was thought to be present in sixteen patients.

Transient pericardial friction rubs were heard in eleven patients, and all of these disappeared within forty-eight hours. In seventeen additional patients a rub was heard later. Accentuated aortic second sounds were heard in seven patients and an accentuated pulmonic second sound in three. A tic-tac rhythm was recorded on three occasions.

Important abnormal pulmonary signs were noted in fifty-one individuals; râles were heard in forty-one patients, in four of whom frothy or bloody sputum was present. In twenty-one patients wheezing noises over the lungs were heard during the acute attack of myocardial infarction, and in most of these instances considerable coughing was observed during the physical examination.

Other important physical signs were noted during the initial physical examinations in Army hospitals. Sweating was noted in 109 patients, pallor in fifty-seven, cyanosis in forty-five, and definite clinical shock in twenty-nine. Seventeen patients were disorientated and confused or in a semiconscious state, and ten other patients groaned or appeared to be choking or suffocating during examination.

Signs of aging were present in forty-two of the men. Twenty-three men were reported as appearing definitely older than their stated ages; eleven others had gray hair; and eight had arcus senilis.

Blood Pressure Records of the Survivors.—There were records of the blood pressure readings both at induction and during the acute attack for 263 survivors. In 108 patients (41 per cent) the blood pressure at induction and the readings during the attack were entirely within the normal limits of 100 to 139 mm. Hg systolic and 60 to 89 mm. Hg diastolic.

Fifty-two patients (20 per cent) had definite elevations of the blood pressure above induction levels, the systolic being 140 mm. Hg or greater and the diastolic, 90 mm. Hg or higher. Thirty-three of these patients had normal pressures at induction, eight had elevated systolic and diastolic readings at induction, six had normal systolic pressures and borderline elevated diastolic pressures (90 or 92 mm. Hg) at induction, and five had elevated systolic and normal diastolic pressures at induction. Of the thirty-three patients with normal systolic and diastolic pressures at induction and elevated pressures during the attack, fifteen had systolic pressures ranging from 140 to 149 mm. Hg, eight from 150 to 159 mm. Hg, five from 160 to 169 mm. Hg, one from 170 to 179 mm. Hg, three from 180 to 189 mm. Hg, and one over 190 mm. of mercury. The last patient had a blood pressure of 118/76 at induction and a pressure of 190/90 during his acute attack. Of this group, the diastolic pressures were between 90 and 99 mm. Hg in sixteen, between 100 and 109 mm. Hg in twelve, and over 110 mm. Hg in five.

In eight patients in whom there occurred a definite rise in systolic and diastolic blood pressures during the "acute attack," as compared with the induction blood pressures, the systolic and diastolic blood pressures were slightly elevated at induction. The diastolic pressures ranged between 90 and 98 mm. of mercury. Of the eight men, four had systolic pressures of 150 and 159 mm. Hg in the acute attack, one between 160 and 169 mm. Hg, one between 170 and 179 mm. Hg, one between 180 and 189 mm. Hg, and one between 190 and 199

mm. of mercury. In the patient with the highest systolic pressure, the blood pressure was 144/96 at induction and 196/114 during the attack. A summary of the increase in the diastolic pressures showed two men to have diastolic pressures between 100 and 109 mm. Hg, four between 110 and 119 mm. Hg, and two of 120 mm. of mercury. The patient with the highest diastolic pressure had a pressure of 144/90 mm. Hg at induction and of 180/120 mm. Hg during the "acute coronary attack."

In six patients in whom there was a normal systolic pressure and a slightly elevated diastolic pressure of 90 to 92 mm. Hg at induction, there was a definite elevation of both systolic and diastolic pressures during the acute attack. In two instances the systolic elevation was between 140 and 149 mm. Hg; in two, between 150 and 159 mm. Hg; in one, 170 mm. Hg; and in the sixth case, 180 mm. of mercury. In the last patient the induction pressure was 130/90 mm. Hg, and the pressure during the attack was 180/110 mm. of mercury. In these six patients the diastolic pressures during the acute attack were, respectively, 96, 120, 100, 100, 110, and 110 mm. of mercury.

Five men who had normal diastolic pressures and slightly elevated systolic pressures on induction showed elevation of both systolic and diastolic pressures during the "acute attack." Two had systolic levels during the acute attack between 150 and 159 mm. Hg, two had levels of 160 mm. Hg, and one, a level of 230 mm. of mercury. The greatest change in this group occurred in a man whose induction pressure was 140/88 mm. Hg and whose pressure during the acute attack was 230/120 mm. of mercury. The diastolic pressures of these men during the acute attack were, respectively, 102, 108, 100, 120, and 120 mm. of mercury.

Twenty-four men showed definite elevation of either the systolic or the diastolic pressure during the acute attack, as compared with the blood pressure at induction. Eighteen soldiers showed an elevation of the diastolic pressure to 90 mm. Hg or higher, and six others had a systolic elevation to 140 mm. Hg or higher. Among the eighteen patients in whom there were diastolic elevations from previous levels to 90 mm. Hg or higher, fourteen had entirely normal induction blood pressures, four had systolic elevations at induction of 140 to 149 mm. Hg, and three had diastolic pressures at induction of 90 to 92 mm. of mercury. Of the eighteen soldiers with elevated diastolic pressures during the "acute coronary attack," nine had elevations from 90 to 99 mm. Hg, eight, from 100 to 109 mm. Hg, and in one the pressure reached 110 mm. of mercury.

In the six soldiers in whom there was an elevation of the systolic pressure alone, the induction blood pressures were normal in four, the systolic pressure 148 in one, and the diastolic pressure 90 mm. Hg in one. During the acute attack the systolic pressure was elevated in four to 140 to 149 mm. Hg, to 158 mm. Hg in one, and to 180 mm. Hg in another. The greatest change in this group was from 148/80 mm. Hg at induction to 180/80 mm. Hg during the acute attack.

Thirty-six men had a definite drop of blood pressure at the beginning of the "acute attack" as compared with induction pressure. In sixteen men the drop brought the systolic pressure to below 100 mm. of mercury. At induction, ten of this group had normal blood pressures, three had slightly elevated systolic and diastolic pressures, two had slightly elevated diastolic pressures, and one,

an elevated systolic pressure. During the early stage of the "acute attack," seven had systolic pressures between 90 and 99 mm. Hg, four between 80 and 89 mm. Hg, one between 70 and 79 mm. Hg, one between 50 and 59 mm. Hg, and three had practically imperceptible pressures. The diastolic pressures in this group also showed a relative drop. In fourteen patients the diastolic pressures were 60 mm. Hg or lower (in three, practically imperceptible) and in two the diastolic pressure was 70 mm. of mercury. In twenty of these thirty-six patients the systolic and diastolic pressures were within the normal range, whereas the pressures at induction were slightly elevated. The pressures in all but three of this group were between 140 and 149 mm. Hg, systolic, and about 90 mm. Hg, diastolic.

In twenty-nine patients there was a drop in the systolic pressure alone during the "acute attack." In nineteen of these the systolic drop was from 140 to 149 mm. Hg at induction to 100 to 139 mm. of mercury. In ten of them there was a definite drop of systolic pressures to a level below the 100 mm. Hg during the "acute attack," whereas the diastolic pressures remained within normal limits.

There were eight patients in whom there was a slight drop in the diastolic pressure during the "acute attack," as compared with the blood pressures at induction. In most of these the drop was very slight, from a borderline level of 90 to 93 mm. Hg to normal levels 10 to 20 mm. Hg lower, as follows: from 130/90 to 108/80, 108/90 to 110/80, 130/93 to 120/70, 112/85 to 100/56, 135/90 to 118/76, 130/90 to 110/70, 130/90 to 122/78, and from 132/92 to 100/50.

During the "acute attack" four men had a slight drop in the systolic pressure and a rise in the diastolic pressure, as compared with the pressures at induction, as follows: from 150/90 to 140/120, 150/90 to 140/96, 140/80 to 118/94, and from 150/90 to 136/120.

Two men had very slight systolic elevations and a slight diastolic drop during the "acute attack," as follows: from 128/90 to 140/84, and from 132/100 to 140/84.

The behavior of the blood pressure in these 263 patients during the "acute attack" may be summarized as follows:

	NUMBER	PER CENT
Remained the same	108	41.1
Systolic and diastolic rose	52	19.8
Systolic and diastolic dropped	36	13.7
Systolic alone rose	6	2.3
Systolic alone dropped	29	11.0
Diastolic alone rose	18	6.8
Diastolic alone dropped	8	3.0
Systolic dropped and diastolic rose	4	1.5
Systolic rose and diastolic dropped	2	0.8
	263	100.0

The subsequent course of the levels of the blood pressures was as follows: Blood pressure readings were available during the entire period of hospitalization for 255 of the 263 survivors who had blood pressure determinations made at the time of induction into the Army and during the acute "coronary attack." There were 179 (70 per cent) in whom the blood pressure remained normal or returned to normal levels within twenty-four hours after the initial hospitalization and continued normal throughout hospital treatment. In fifty-six men (22 per cent) in whom there was either an elevation or lowering of blood pressure readings from normal levels of 100 to 140 mm. Hg systolic and 60 to 90 mm. Hg diastolic during the "acute attack," normal levels were reached after a period of forty-eight hours or longer following the onset. Twenty patients (8 per cent) showed constantly elevated or lowered blood pressures during the period of convalescence following the acute "coronary attack"; eleven patients had "low" blood pressures and nine revealed varying degrees of arterial hypertension.

Among the 108 patients in whom there was no apparent change in the blood pressure levels found at induction and the levels observed during the acute attack, the levels remained normal throughout the entire convalescent period of eighty-five. In the same group the blood pressure levels in twenty patients fell below the normal range after the "attack" but returned to normal levels at varying times during convalescence. In these twenty patients with transient subnormal blood pressure levels the following time relations may be of interest. Two showed a drop of blood pressure twelve hours after the first normal blood pressure was noted in the "acute attack," and in both instances the blood pressure reached normal levels in three days. In seven patients the drop in blood pressure occurred twenty-four to forty-eight hours after the onset of the "attack" and remained at low levels for varying periods of time; in two, the pressures were low for one day, in two, for three days, in one, for four days, in one, for seven days, and in one the pressures were low for six weeks. In eleven soldiers the initial blood pressure drop occurred from four to six days after the onset and remained at low levels from periods varying from three days to six weeks before returning to normal. In two others the blood pressure dropped to subnormal levels within forty-eight hours after the onset of the attack and remained below normal throughout the remaining period of Army medical observation. In another patient an elevated blood pressure was noted on the eighth day after the "attack," and this elevation persisted.

In forty-nine of the fifty-two patients in whom there was definite elevation of the systolic and diastolic blood pressure during the acute "coronary attack," as compared with known previous blood pressure levels, frequent blood pressure determinations were available during convalescence. In thirty patients the elevated blood pressures returned to normal levels within twenty-four hours after the onset and remained normal; in eleven others normal blood pressure levels were reached at a longer period of time after the onset of the "attack." In this latter group of eleven men, normal levels were attained after forty-eight hours in six patients, after seventy-two hours in one, after ninety-six hours in two, after six days in one, and after six weeks in one patient. Three men showed an elevation of blood pressure levels during the acute "attack" and also through-

out the period of convalescence; two others experienced a drop of blood pressure to very low levels within twenty-four hours after the onset of the attack, and in each instance the blood pressure remained low. In three other soldiers the elevated pressure noted early in the acute phase of the attack dropped to very low levels for five to seven days before returning to a normal range.

Adequate follow-up blood pressure readings were available for analysis in all thirty-six patients who showed a drop in the systolic and diastolic blood pressures during the acute "coronary attacks." In twenty-three men the blood pressure returned to normal levels within twenty-four hours and remained normal throughout the long period of convalescence. In ten men the pressures ultimately returned to normal after a period of forty-eight hours or longer with low blood pressure levels; in three men the pressure returned to normal levels in forty-eight hours, in one man in five days, in one man in six days, in one man in eight days, in two men in three weeks, and in two men in six weeks. In the three remaining patients the low blood pressure noted during the acute "coronary attack" persisted throughout the entire period of hospitalization.

There were twenty-eight patients in whom blood pressure determinations were available following the acute "coronary attack" who, during the attack, showed a definite drop in the systolic blood pressure levels. In eighteen patients the blood pressures, both systolic and diastolic, were normal within twenty-four hours after the onset of the acute attack and remained normal throughout the remainder of hospitalization. Six soldiers showed normal blood pressure levels after forty-eight hours or longer of low systolic levels; in one man the pressure returned to normal in forty-eight hours, in two men in seventy-two hours, in one man in five days, in one man in thirteen days, and in one man in fourteen days. In two other patients the low systolic pressure remained below 100 mm. Hg throughout the period of hospitalization; and in two others, after forty-eight hours of low blood pressures a persistent hypertension developed.

Five of six patients with an elevated systolic and a normal diastolic blood pressure during the acute "coronary attack" within twenty-four hours had normal blood pressures that persisted throughout hospitalization. In the sixth patient the blood pressure remained elevated.

Follow-up blood pressure determinations were available in sixteen patients in whom there was an elevation of the diastolic blood pressure during the acute coronary attack. In eleven instances the diastolic pressure had returned to normal levels within twenty-four hours after the acute attack and remained normal throughout further hospitalization. In one instance the diastolic and systolic blood pressures dropped to below the normal range and remained low during hospitalization; in another the blood pressures at first returned to normal levels, and then both systolic and diastolic pressures became constantly elevated. In the three remaining patients of this group the diastolic blood pressure remained elevated for thirty-six to seventy-two hours and then returned to normal levels; in two of these patients an occasional drop in the systolic and diastolic blood pressures was observed between the third and eighth weeks of treatment.

The changes in blood pressure observed in conjunction with and following occlusion in this group of patients may be compared with the experience of others.

Levine and Brown[102] stated that the blood pressure occasionally remained high with occlusion, but the higher the blood pressure, the more marked was the fall of pressure in most cases. Allen[125] observed that the blood pressure usually fell within the first seventy-two hours but that this fall might be delayed in rare cases for ten days to two weeks. The pressure stayed down for more than a few hours, and if it had been 200 mm. Hg or more it went down to 110 to 120 and remained there for weeks; the prognosis had to be guarded until it assumed a higher level. It rarely returned to 200 mm. but generally rose to 150 to 175 and remained there, recovery usually being delayed until the blood pressure had reached its normal or nearly normal level. When blood pressure was above normal before the fall occurred the outlook was better than when it was within the normal range. Palmer[105] stated that changes in the blood pressure and the height of the blood pressure following recovery from an attack of coronary thrombosis were, on the whole, of little significance. Weiss[126] commented that although a fall in blood pressure has been given as one of the most important criteria for differentiating coronary artery occlusion from angina pectoris, a brief initial rise may occur in the former, and he reported three cases showing an early rise in pressure. He quoted Fishberg to the effect that shock or peripheral circulatory failure predominated in the first days of coronary thrombosis in individuals who had previously had slight symptoms or no symptoms of cardiac insufficiency and made the observation that in the initial stage of traumatic shock the arterial pressure may rise as a consequence of arteriolar constriction in the extremities before it falls. He also quoted Mendlowitz, Schauer, and Gloss, who suggested, on the basis of animal experiments, that for a brief period following coronary occlusion a peripheral vasoconstriction occurred to compensate for the coincident diminution in cardiac output. Master and associates[110] noted that occasionally the onset of coronary occlusion in patients with severe pain was associated with a transitory rise of blood pressure which sometimes reached 200 mm. of mercury. However, they stated that the pressure always fell during the attack, rapidly in 57 per cent and gradually in 42.5 per cent; occasionally a week or more elapsed before a significant fall became evident. The most rapid fall seemed to occur in nonhypertensive patients in whom the attack was fatal. The actual fall in pressure depended largely upon the initial level; 20 per cent who survived had an initial systolic pressure of 200 mm. Hg or more and the pressure did not fall below 150, and in the group with pressures of 150 to 190 mm. Hg, a fall below 150 mm. occurred in all but 3 per cent and below 100 mm. in 30 per cent. The diastolic pressure followed the same trend as the systolic, but the drop was less precipitate and less marked. Chambers[111] found that in 63 per cent of 100 cases of infarction there was an initial fall of blood pressure, in 32 per cent no change, and in 5 per cent an initial rise. All of the patients in the last group had hypertension and of these only one survived. The fall in blood pressure usually remained within hypertensive levels and it was immediate or delayed as long as seven days. They regarded an early return to normal or preocclusional levels as a good prognostic sign; the blood pressure usually did not return to former levels in the fatal group. The number of survivors regaining hypertension after the occlusion increased with time; 58 per cent had done so by the second year. After

recovery the height of the blood pressure had no effect on the frequency of recurrence of infarction or ultimate prognosis. All of the articles quoted included observations on both male and female patients.

DISCUSSION OF SYMPTOMATOLOGY

Reference to the literature on the symptomatology of coronary artery disease with acute occlusion shows, as is generally known, that pain is the commonest and most prominent symptom of the attack. For instance, in Howard's[46] series of 165 cases, pain occurred in 93 per cent; Kennedy[127] reported pain to be absent in only 4 per cent of 200 cases, with so-called classical pain in 91 per cent of the cases of recent infarction; Bean[128] found pain to be present in 75 per cent of 104 first attacks and 66 per cent of forty second attacks; Herrmann and Dechard[129] recorded pain in ninety-five of 127 cases; Babey[130] found pain to be absent in only one of 116 cases; Pollard and Harvill[71] reported 375 cases, in 353 of which pain was present; Rosenbaum and Levine[131] found pain to be absent in only 3 per cent of 208 cases, and Kugel[83] saw less than 3 per cent of 350 cases without pain. On the other hand, much has been written on the subject of painless coronary occlusion. Thus, Davis[132] found pain to be absent in twenty-nine of seventy-six cases, and in these the onset was abrupt with dyspnea. Other authors have noted that pain is likely to be absent in patients in whom dyspnea is a prominent symptom or in whom congestive failure is present.[1,92,129,133,134] However, as pointed out by Bean,[128] pain and congestive failure are not mutually exclusive; and Smith and associates[135] stated that sooner or later pain and dyspnea are commonly combined.

Hammon[136] observed that the pain of acute coronary artery occlusion is more circumscribed than the pain of angina pectoris; we doubt, however, whether this holds true sufficiently often to be helpful. Descriptions in the literature of the nature of the pain are similar to those given in our series. It appears also that radiation of the pain is not so common as is generally believed. For instance, among Nathanson's[34] 113 cases the pain radiated from the sternal, precordial, or epigastric region in only 10 per cent, and in Bean's[128] 300 cases there was no radiation in seventy.

Willius[60] emphasized the occurrence of anginal pain before the attack. It was present in eighty-three of 370 cases two weeks to fifteen years before the acute occlusion and persisted or appeared after occlusion in 167 cases; it was present before occlusion in twenty-seven in which it did not recur after occlusion. Previous angina was present in forty-two of Bean's[128] 300 cases. Smith, Sauls, and Ballew[75] reported angina both before and after occlusion in thirty-three of 100 cases; only before the attack in thirteen cases, and only after the attack in twenty-three cases. Fisher and Zukerman[137] noted previous angina in forty-five of 108 cases.

The subject of premonitory or preliminary pain has been discussed by Feil,[138] Sampson and Eliaser,[66] Master and associates,[119] and others. There is no way of knowing, however, when such pains are the precursor of acute myocardial infarction. The whole matter is tied in with the differentiation of

classical angina and so-called attacks of coronary insufficiency. If angina of effort, which began insidiously, has become established in a patient, one may feel relatively safe in assuming that the angina does not forbode an attack of myocardial infarction, although the possibility of infarction in such cases is always present. On the other hand, isolated attacks of anginoid pain, particularly when not induced by exertion and when accompanied by sweating, should always be considered of serious import and the patient treated as if an acute myocardial infarction were imminent. These are the cases in which the question of whether to use Dicumarol is important; it is probably more important to use it in such cases than in those in which the diagnosis of acute myocardial infarction has been made. An objection to its use, however, is that the likelihood of intimal hemorrhage might be increased, This we are inclined to doubt.

The prominence of epigastric pain has been noted repeatedly. It is merely a variant of substernal pain. Nathanson[34] reported epigastric pain in 25 per cent of 113 cases; Howard,[46] in 13.3 per cent of 165 cases; Bean,[128] in twenty-nine of 300 cases; Smith and associates,[75] in fifty of 100 cases; and Fisher and Zukerman,[137] in eight of 108 cases.

The foregoing data from the literature were based on series of patients of all ages. Goodson and Willius,[68] in a report of thirty patients under 40 years of age, noted a preceding anginal syndrome (one day to six months) in eight. Three of these patients experienced no pain with the attack.

Dyspnea, the symptom of the attack which we observed next most commonly, appears also to be the next most common one in published series of cases. It is probably due to some degree of left ventricular failure and is often confused with the pain, in that a feeling of suffocation may be interpreted either as pain or as difficulty in breathing. Hammon[136] stated that dyspnea is seldom absent, Wolff and White[1] reported dyspnea in almost all of twenty-three cases. Parkinson and Bedford[40] found that dyspnea and failure without pain characterized one of their clinical groups based on eighty-three cases, the other two being sudden death and prolonged anginal pain with shock. Of Howard's[46] 165 patients, sixty-four had dyspnea. In the series of 420 cases studied by Smith and co-workers,[135] dyspnea was present in 189 and paroxysmal dyspnea in thirty-five. Rosenbaum and Levine[131] reported dyspnea in 71 per cent of 208 cases. In fifty-nine of 108 cases reviewed by Fisher and Zukerman,[137] there was dyspnea; in five, orthopnea; in two, persistent cough; and in one, hemoptysis. In Bean's[128] comprehensive study of 300 cases, dyspnea was present before the attack in eighty-five; paroxysmal nocturnal dyspnea, in thirty; and orthopnea, in forty-seven. In the first coronary attack 95 per cent of patients had dyspnea, 68 per cent had orthopnea, and 24 per cent had Cheyne-Stokes breathing; in the second attack 96 per cent had dyspnea, 63 per cent had orthopnea, and 71 per cent had Cheyne-Stokes respiration. In reviewing the past history of 235 cases of coronary thrombosis, Phipps[139] found that twenty-one patients had only dyspnea and seventeen had paroxysmal nocturnal dyspnea, while forty-seven had "myocardosis, a symptom-complex of dyspnea, palpitation and precordial discomfort or pain." He stated, "Dyspnea, otherwise unexplained, and marked on slight exertion in a middle-aged individual, is more than suggestive of underlying coronary disease."

Various authors have commented on nervous manifestations. Wolff and White[1] stated that restlessness is characteristic. Syncope and convulsions have been noted. Cookson[140] found syncope or epileptiform attacks in fifteen of 200 cases. Herrmann and Dechard[129] reported syncope in five of 127 cases.

Vasomotor symptoms and/or shock are common. The highest percentages reported were by Rosenbaum and Levine[131]; among 208 cases, shock was present in 54 per cent, and cyanosis, in one-half of the cases; sweating also was common. Hammon[136] noted that blanching and sweating are common and that transient sweating is sometimes observed.

Gastrointestinal symptoms are also common. Parkinson and Bedford[40] found vomiting to be usual after the onset and sometimes repeated for days. Howard[46] reported vomiting in 28 per cent of his cases; Bean,[128] in 59 per cent in both first and second attacks. A few other authors found much smaller percentages of vomiting. Phipps[139] noted previous indigestion in nineteen of 235 cases. Hammon[136] observed that epigastric pain was often associated with tenderness and rigidity, nausea, and vomiting; in such cases differential diagnosis may be difficult. Diarrhea was noted by some authors.

We have selected Bean's[128] data from 300 cases with autopsy as most comparable with ours. His figures on the symptomatology are as follows:

SYMPTOMS PRIOR TO THE INITIAL INFARCT (125 CASES OF BEAN'S SERIES)

	NUMBER OF CASES	%
Dyspnea or exertion	88	70
Weakness	67	54
Cough	51	41
Nocturia	50	40
Orthopnea	47	38
Ankle edema	44	35
Angina pectoris	42	34
"Indigestion"	35	28
Paroxysmal nocturnal dyspnea	30	24
Palpitation	30	24
Syncope, fainting spells	28	22
Users of digitalis	18	14
Hemiplegia	11	9
Users of nitroglycerin	9	7
Auricular fibrillation	2	2

Painful prodromal symptoms appeared twenty-eight times. They were observed only twice before a second infarction and in no subsequent attacks.

SYMPTOMS OF THE ACUTE ATTACK IN BEAN'S SERIES

	FIRST ATTACK		SECOND ATTACK	
	NUMBER OF CASES	%	NUMBER OF CASES	%
Dyspnea	114	95	67	96
Enlarged heart	72	83	53	85
Weak heart sounds	77	85	56	82
Râles	91	83	54	82
Cyanosis	69	77	44	86
Cough	32	70	27	84
Pallor	38	69	26	79
Pain	104	75	40	66
Orthopnea	66	68	37	63
Sweating	31	60	15	60
Vomiting	47	59	16	59
Ankle edema	58	55	32	54
"Shock"	79	57	34	45
Restlessness	50	44	37	49
Tachycardia (rate over 108)	43	42	32	48
Systolic murmur	38	38	24	39
Cheyne-Stokes respiration	25	24	25	71
Ascites	11	26	14	42
Cloudy sensorium	41	26	16	33
Enlarged liver	11	18	7	23
Gallop rhythm	12	12	11	27
Prodromal phenomena	28	21	2	4
Bradycardia (rate below 80)	16	16	10	15
Angor animi	17	12	8	20
Pericardial friction rub	17	15	7	6
Pulsus alternans	10	9	6	14
Precordial hyperesthesia	8	8	3	8
Jaundice	6	6	5	10
Anuria	8	4	—	—
Hiccough	4	2	—	—
Uremia	3	2	—	—

ORIGINAL SITE OF PAIN (BEAN'S SERIES)

	NUMBER OF CASES
Substernal	88
Epigastric	29
Precordial	21
Left shoulder	5
Back	1

RADIATION OF PAIN (BEAN'S SERIES)

	NUMBER OF CASES
None	70
Left arm	23
Both arms	13
Both arms and both shoulders	8
Left arm and shoulder	8
Left arm and both shoulders	3
Right chest	3
Right arm	2
Left shoulder	2
Angle of scapula	2
Right shoulder	1
Left arm and jaw	1
Neck and jaw	1
Both arms and back	1
Back	1

TYPES OF PAIN (BEAN'S SERIES)

	NUMBER OF CASES
Crushing pressure	44
Squeezing, constricting, vicelike	29
Choking, smothering, suffocating	18
Sharp, stabbing, knifelike	11
Sore, aching, dull	11
"Excruciating"	7
Burning	5

Bean then lists fourteen categories of what he calls substitution symptoms which are reminiscent of the symptoms in some cases of our series:

SUBSTITUTION SYMPTOMS IN BEAN'S SERIES

SYMPTOMS	NUMBER OF CASES
Sudden onset of cardiac asthma, orthopnea, or pulmonary edema	11
Gradual increase in congestive failure	9
Sudden increase in severity of preexisting failure	6
Weakness and syncope	4
Sudden onset of dyspnea and edema	4
Sudden onset of suffocation and choking	2
Sudden onset of palpitation, auricular fibrillation present	2
Vomiting, dizziness, and dyspnea	1
Angor animi and cardiac asthma	1
Dyspnea, weakness, and nervousness	1

SUBSTITUTION SYMPTOMS IN BEAN'S SERIES—(CONTINUED)

SYMPTOMS	NUMBER OF CASES
Dyspnea, weakness, and syncope	1
Severe weakness and increase in failure	1
Weakness and dizziness	1
Paralysis of left arm, paresthesia; no pain	1

The physical examinations in Bean's[128] series showed many more clinically demonstrable enlarged hearts than in our series, but the incidence of pre-existing hypertension in his series is not ascertainable, although it was probably much greater than in ours. Auricular fibrillation was also much more common in his series, occurring in thirty-five cases. A pericardial friction rub was heard in twenty-four cases of 176 (14 per cent), as against twenty-eight cases among our 400 survivors (7 per cent). As in our group of survivors, Bean found that the blood pressure remained elevated in a large number of cases, although the majority showed declining levels.

A pericardial friction rub was found in 10 per cent of Howard's[46] 165 cases, in 16 per cent of the 208 cases of Rosenbaum and Levine,[131] in 20 per cent of Levy's[141] fifty cases, and in only one of the 108 cases of Fisher and Zukerman.[137]

Electrocardiograms of the Survivors.—Electrocardiograms were taken in every case; in fact, no case was included in this study unless there was adequate electrocardiographic evidence to corroborate the clinical diagnosis of myocardial infarction. All of the original electrocardiograms were studied. In most instances the electrocardiograms were typical of recognized patterns associated with known myocardial involvement. The classical pattern representing anterior myocardial infarction was present in 176 instances (44 per cent), and the typical pattern of posterior infarction was noted in 113 instances (28 per cent). In fifty-six patients (14 per cent) the electrocardiogram was considered indicative of lateral, anteroposterior, posterolateral, or anterolateral infarction. Abnormal tracings without characteristic localizing features were present in fifty-five individuals (14 per cent), but in this group the electrocardiograms were considered as adequate to substantiate the clinical diagnosis of myocardial infarction. Thus, it is seen that there were more than one-half as many cases of posterior infarction as of anterior infarction among the survivors. This ratio may be compared with that shown subsequently of less than one-third as many cases of thrombosis of the right coronary artery as of the left anterior descending artery among the fatal cases, a difference which may serve to substantiate to some extent the statement sometimes made that occlusion of the right coronary artery is not so serious as occlusion of the left anterior descending artery.

Follow-up electrocardiograms* were taken during examinations made by the Veterans Administration, and in 353 of the original 400 patients these tracings

*Most of the electrocardiograms were made with the three standard leads and usually one or two precordial leads (CF_2 and CF_4 or CF_5).

were available for study. In addition, electrocardiograms from the other forty-seven patients, taken three to four months after the initial attack of myocardial infarction, were available. Electrocardiographic evidence of residuals of myocardial infarction was present in 366 (92 per cent) of the patients, while in thirty-four (9 per cent) instances the follow-up electrocardiogram was regarded as within the normal range. The break-down in the group of electrocardiograms which returned to normal was as follows: of 176 anterior infarctions, fourteen returned to normal; of 113 posterior infarctions, six returned to normal; of fifty-six lateral, anteroposterior, and posterolateral infarctions, four returned to normal; and in the fifty-five without localizing features, ten returned to normal.

Roentgenologic Evidence Among the Survivors.—Roentgenograms of the heart were taken in 394 of the 400 men during the first hospitalization for treatment of heart disease. In 314 instances (79 per cent of the entire group with roentgenographic examinations), the heart was considered to be of normal size and shape. In the remaining eighty patients the heart was considered enlarged, with seventy-eight instances of left ventricular enlargement and two of right and left ventricular enlargement. In four men pericardial effusion was diagnosed from the roentgenograms. Following fluoroscopy, pleuropericardial adhesions were suspected in three patients, and in five patients myocardial infarction of the left ventricle was suspected.

Pulmonary abnormalities were noted in the roentgenograms in twenty-one soldiers: bilateral pulmonary congestion was diagnosed in twelve patients, unilateral pulmonary infiltration in five, pulmonary infarction in three, and left pleural effusion in one patient. In all instances the pulmonary lesions cleared up.

From a roentgenographic point of view the aorta was considered abnormal in twenty-one subjects; in nine cases there was simple widening and in eleven, definite tortuosity. In only one patient was a calcified plaque demonstrated in the aorta.

Temperature, White Blood Cell Count, and Sedimentation Rate.—In the series of 400 survivors temperature records were available in 370 patients, leucocyte counts in 396, and sedimentation rates in 379, but all three of these studies were recorded in only 274 patients during the "acute attack" and, thereafter, sufficiently often to be valuable for correlation of all three factors.

In these 274 cases the temperature records were adequate for review. There were fifty afebrile patients. In seventy patients the highest temperature reached during the "attack" was between 99 and 99.9° F.; in 129 patients, between 100 and 101.9° F.; and in 25 patients the temperature reached 102° F. or more. When fever was present the temperature curve followed a definite pattern. The temperature started to rise in four to forty-eight hours following the onset of symptoms and reached the peak of elevation in another twenty-four to thirty-six hours. It returned to normal by lysis in another forty-eight to seventy-two hours. The temperature was normal by the ninth day after the onset of the attack in all but one instance in which the course was complicated by acute thrombophlebitis of the right leg.

The white blood cell count remained entirely within the normal range in fifty-five of the 274 soldiers throughout the period of hospitalization. There were thirty-eight patients with slightly increased white blood cell counts (9,000 to 10,000 per c. mm. of blood), 163 with moderately increased counts (11,000 to 19,000 per c. mm. of blood), and eighteen with high white blood cell counts (over 19,900 per c. mm. of blood). In 69 per cent of the patients the count reached its highest value wihin twenty-four hours of the onset of the attack and prior to the peak value of the sedimentation rate. In 15 per cent the highest leucocyte count was noted during the second day, and in the remaining 16 per cent the greatest white blood cell count appeared from the third to the eleventh day, the majority of these being on the third and fourth days. The majority of the counts (83 per cent) returned to the normal range within the first twelve days after the onset of the attack. In the remaining 17 per cent the count reached normal two weeks or more after the onset, and in more than two-thirds of these, before the end of the third week. In two patients the count remained slightly elevated throughout the period of hospitalization. The curves of rise and decline of the white blood cell count were similar whether the count was slightly elevated, moderately elevated, or high at the peak.

In fifty-eight of the 274 patients the sedimentation rate remained normal throughout the period of hospitalization; in twenty-three patients the rate became slightly increased (13 to 16 mm. per hour), in eighty-eight patients it became moderately increased (17 to 29 mm. per hour), and in 105 patients it became greatly increased (30 mm. or more per hour). The time interval between the onset of the attack and the day on which the sedimentation rate was greatest varied considerably and had no apparent relationship to the degree of leucocytosis and/or the height of the temperature elevation. In 72 per cent of the patients with increased sedimentation rates the greatest increase in rate occurred from the first to the ninth day after the onset of symptoms, with an almost even distribution for the days of this period. In 20 per cent of the patients with increased rates the greatest increase occurred between the tenth and fifteenth days after the onset of the attack. In the remaining 8 per cent the greatest increase in rate occurred at various intervals from the nineteenth to the fifty-second day.

The time interval between the onset of the attack and the return of the sedimentation rate to the normal range varied greatly and did not assume any characteristic pattern, although there was a tendency for the rate to return to normal between the fifteenth and the fortieth days after the onset (53 per cent). The return to normal occurred within the first two weeks in very few instances (7 per cent). In some patients (22 per cent) the return to normal occurred only after a prolonged period of hospitalization (as much as 119 days). In the remaining 18 per cent of the patients the sedimentation rate remained increased throughout the period of hospitalization.

In regard to the correlation between the degree of increase of the sedimentation rate and the time at which the greatest increase occurred and the time of return to normal, there was no significant difference among the three groups, although there was a slightly increased tendency for those patients with the

greatest increase in rate to have a longer period before return of the rate to normal.

A comparison was made of the three factors of temperature, white blood cell count, and sedimentation rate. The results are shown in Tables XXV, XXVI, and XXVII.

TABLE XXV. TEMPERATURE IN RELATION TO WHITE BLOOD CELL COUNT AND SEDIMENTATION RATE DURING ACUTE MYOCARDIAL INFARCTION OF SURVIVORS

	TEMPERATURE							
	AFEBRILE		99 TO 99.9°F.		100 TO 101.9°F.		102°F. OR MORE	
	NO.	%	NO.	%	NO.	%	NO.	%
White Blood Cell Count								
Normal	17	34	23	33	15	12	0	0
9,000 to 10,000	13	26	13	19	10	8	2	8
11,000 to 19,000	19	38	32	45	92	71	20	80
20,000 and over	1	2	2	3	12	9	3	12
Total	50	100	70	100	129	100	25	100
Sedimentation Rate								
Normal	16	32	22	31	17	13	3	12
13-16 mm./hr.	8	16	5	8	9	7	1	4
17-30 mm./hr.	18	36	21	30	45	35	4	16
31 mm./hr. and over	8	16	22	31	58	45	17	68
Total	50	100	70	100	129	100	25	100

TABLE XXVI. WHITE BLOOD CELL COUNT IN RELATION TO SEDIMENTATION RATE AND TEMPERATURE DURING ACUTE MYOCARDIAL INFARCTION OF SURVIVORS

	WHITE BLOOD CELL COUNT							
	NORMAL		9,000 TO 10,000		11,000 TO 19,000		20,000 AND OVER	
	NO.	%	NO.	%	NO.	%	NO.	%
Sedimentation Rate								
Normal	19	34	12	32	25	15	2	11
13-16 mm./hr.	3	6	7	18	11	7	2	11
17-30 mm./hr.	18	33	9	24	58	35	3	17
31 mm./hr. and over	15	27	10	26	69	43	11	61
Total	55	100	38	100	163	100	18	100
Temperature								
Afebrile	17	31	13	34	19	12	1	5
99-99.9°F.	23	42	13	34	32	20	2	11
100-101.9°F.	15	27	10	27	92	56	12	67
102°F. or more	0	0	2	5	20	12	3	17
Total	55	100	38	100	163	100	18	100

TABLE XXVII. SEDIMENTATION RATE IN RELATION TO WHITE BLOOD CELL COUNT AND TEMPERATURE DURING ACUTE MYOCARDIAL INFARCTION OF SURVIVORS

	SEDIMENTATION RATE							
	NORMAL		13 TO 16 MM./HR.		17 TO 30 MM./HR.		31 MM./HR. AND OVER	
	NO.	%	NO.	%	NO.	%	NO.	%
White Blood Cell Count								
Normal	19	33	3	13	18	20	15	14
9,000 to 10,000	12	21	7	30	9	10	10	10
11,000 to 19,000	25	43	11	48	58	66	69	66
20,000 and over	2	3	2	9	3	4	11	10
Total	58	100	23	100	88	100	105	100
Temperature								
Afebrile	16	27	8	35	18	20	8	8
99 to 99.9°F.	22	38	5	22	21	24	22	21
100 to 101.9°F.	17	30	9	39	45	51	58	55
102°F. or more	3	5	1	4	4	5	17	16
Total	58	100	23	100	88	100	105	100

The general picture, therefore, was one of elevated temperature, leucocytosis, and increased sedimentation rate. Of the 274 patients studied on the basis of these factors, there were 226 with increased temperatures, 220 with elevated white blood cell counts, and 216 with increased sedimentation rates, the incidence of these abnormal findings being approximately the same for each of the three factors. The correlation among the three factors was significant. They were jointly abnormal in 159 (58 per cent) of the patients; in seventy-six (28 per cent) of the patients two of the factors were abnormal; and in thirty-three (12 per cent) of the patients one of the factors was abnormal. There was no tendency noted for any one pair of factors to occur more often than any other pair, or for any one factor to occur singly more often than any other factor. There were only six (2 per cent) of the patients with normal values for all three factors. Thus, it appears that, typically, elevation of at least one of the three factors should occur during the course of acute myocardial infarction, and most often, that joint elevation of all three factors will be found. The following tabulation summarizes the interrelationship of the three factors in the 274 patients:

NUMBER OF PATIENTS WITH:	SEDIMENTATION RATE NORMAL	SEDIMENTATION RATE INCREASED	TOTAL
Normal temperature and normal white blood cell count	6	11	17
Normal temperature and increased white blood cell count	10	21	31
Increased temperature and normal white blood cell count	12	25	37
Increased temperature and increased white blood cell count	30	159	189
Total	58	216	274

Other Laboratory Tests.—

Urinalysis: In all 400 cases of the survivors, at least one routine urinalysis was made during hospitalization. In sixty instances there were abnormal findings. Albuminuria was present in thirty patients, erythrocytes in twenty-four, casts in twenty (hyalin in seven, granular in nine, and both in four), and sugar in two. Albumin and red blood cells were found together in thirteen patients, albumin and granular casts in three, albumin and hyalin casts in three, and red blood cells and hyalin casts in one.

Blood Sugar Levels: In sixty-five patients blood sugar determinations were made during or within a few days of the acute attack. In all, the results were within normal limits. In seven of the sixty-five cases glucose tolerance tests were performed and all were normal.

Blood Nonprotein or Urea Nitrogen Estimation: These tests were performed in fifty-five patients and were entirely normal in fifty. In five patients the blood nonprotein nitrogen was elevated: 45, 46, 47, 8, 87, and 92 mg. per cent, respectively; all of these elevations occurred during the acute attack. In all five patients the levels returned to normal during the period of initial hospitalization.

Blood Cholesterol Determinations: In sixty-six patients the blood cholesterol level was determined during or shortly after the acute attack. A range of 150 to 250 mg. per cent being considered normal, the levels were normal in forty-three instances and elevated in twenty-three. In eight patients the levels were between 265 and 300; in nine, between 299 and 350; in three, between 349 and 400; in one, at 400; in one, at 450; and in one, at 505 mg. per cent.

CLINICAL COURSE OF THE SURVIVORS

General Features.—All of the men who survived an attack of acute myocardial infarction were observed and treated in an Army Hospital before discharge from service. Two hundred twenty-nine patients (57 per cent of the entire group) had an uneventful convalescence and were entirely asymptomatic after recovery from the "acute attack." The most common symptom was recurrent pain, usually substernal, precordial, or limited to the left side of the chest. These attacks of pain occurred in ninety-eight, 25 per cent of the patients; but in only nine instances could these attacks of pain be considered of major importance and probably representative of the occurrence of a fresh attack. In the majority of patients the pain was of anginal type and associated with increased activity after the patient became ambulatory. In twenty-seven patients (7 per cent) the clinical course during the Army hospitalization could be considered as "stormy," inasmuch as the patients were critically ill and the outcome uncertain for days and weeks. Myocardial insufficiency was considered to be present in twenty-two men, in six of whom there was frank cardiac decompensation with edema of the lower extremities, enlarged liver, or other abnormalities. In sixteen men of the group with myocardial insufficiency, pulmonary congestion was the complicating clinical feature, and in three of these patients, pleural effusions were present. All patients with congestive heart failure recovered from the cardiac decompensation.

Transient pericarditis was noted in twenty-eight instances; in one of these, pericardial effusion developed.

In the order of their frequency the clinical features of the "acute attack" during hospitalization were as follows:

Recurrent pain	98
Pericarditis	28
"Stormy course"	27
Heart failure	22
Pulmonary congestion only	16
Frank failure	6
Dyspnea without râles	19
Vomiting (not associated with drugs)	12.
Sweating	11
Weakness and tiredness	10
Confused, psychotic, disoriented state	6
Numbness of extremities	6
Palpitation	6
Restlessness (marked)	6
Pulmonary infarction	5
Pneumonia (with both clinical and x-ray evidence)	5
Smothering sensation	4
Dizziness	3
Pleural effusion	3
Unconsciousness	3
Abdominal distension	2
Orthopnea	2
Nausea	1
Paresis of arms (transient)	1
Blanching of left leg	1

In twelve instances other specific disease states were found to have existed or developed during hospitalization, as follows:

Exfoliative dermatitis	1
Mumps	1
Polycystic kidney disease	1
Carotid sinus syndrome	1
Fröhlich's syndrome	1
Gout	1
Thrombophlebitis	1
Infectious mononucleosis	1
Diabetes mellitus	1
Hypothyroidism	1
Hydronephrosis with double ureter	1
Acute respiratory infection	1

First Clinical Diagnosis in the Patients Who Survived.—An analysis was made of the first clinical impression or diagnosis given in the 400 patients who were finally diagnosed as having coronary thrombosis or myocardial infarction. In 283 patients (71 per cent) the initial clinical impression was in agreement with the final diagnosis. In eighty-one patients (20 per cent) coronary arteriosclerotic

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heart disease was not regarded as a clinical possibility and an entirely different diagnosis was made. A study of these various diagnoses reveals a long list of the conditions that should be considered in the differential diagnosis of coronary thrombosis or myocardial infarction. In thirty-six patients (9 per cent) no diagnosis was offered at the time of the first recorded clinical examination; in these patients coronary artery disease was apparently never considered as a clinical possibility.

In many records lengthy discussions as to the diagnostic possibilities were made by the ward surgeons, and from these data two definite trends were noted. In many instances the clinical picture was so obviously the classical one of acute coronary thrombosis with myocardial infarction that in spite of the relatively early age of the patient no other diagnosis was even suggested. On the other hand, many examiners felt that although the clinical picture resembled that of coronary thrombosis, such a diagnosis was precluded by the relative youth of the patient.

Diagnoses considered previous to arrival at the final diagnosis of acute coronary artery occlusion and myocardial infarction are listed as follows:

Primary Diagnoses Other Than Coronary Artery Disease

Pleurisy	10
Gastritis	10
Psychoneurosis	9
Essential hypertension	5
Peptic ulcer	5
No heart disease	4
Rheumatic heart disease	4
Pericarditis, acute	4
Neurocirculatory asthenia	3
Nasopharyngitis	3
Diaphragmatic hernia	3
Pneumonia	3
Heat exhaustion	2
Functional heart disease	2
Cardiac arrhythmia	2
Bronchitis, acute and chronic	2
Volvulus	1
Spontaneous pneumothorax	1
Cholelithiasis	1
Dissecting aneurysm	1
Bronchial asthma	1
Malaria	1
Myalgia, pectoral	1
Cardiospasm	1
Intercostal neuralgia	1
Pulmonary pathology	1

SECONDARY DIAGNOSES OTHER THAN CORONARY ARTERY DISEASE

Psychoneurosis	2
Cardiac arrhythmia (noncoronary)	2
Intercostal neuralgia	2
Pleurisy	2
Sliding acquired hernia	1
Hiatus hernia	1
High intestinal obstruction	1
Acute cholecystitis	1
Cholelithiasis	1
Acute gastritis	1
Acute gastric ulcer	1
Esophageal pathology	1
Pneumonia	1
Lung cyst	1
Pulmonary edema	1
Bronchitis, acute	1
Pericarditis	1
Essential hypertension	1
Endocarditis (possible)	1
Cerebral angiospasm	1
Herpes	1
Left perinephritic abscess	1
Congenital heart disease	1

SUBSEQUENT COURSE OF THE SURVIVORS

All of the 400 survivors have come under the jurisdiction of the Veterans Administration for purposes of treatment and pension. They have been examined by cardiologists in the various outpatient departments and/or hospitals of the Veterans Administration. Detailed histories, physical examinations, and laboratory investigations have been made, and in 334 cases complete records were available; in the remainder some data were also available.

The 400 men were treated in Army hospitals for six weeks to eight months and were discharged from the service only after the apparent maximal benefit of hospitalization had been attained, every one being ambulatory. Subsequently two patients have been followed for less than one year, 154 for twelve to twenty-three months, 175 for twenty-four to thirty-five months, fifty-six for thirty-six to forty-seven months, and thirteen for more than forty-eight months.

Since discharge from the Army, forty-eight veterans have had to be hospitalized for treatment of the cardiac condition; seventeen have experienced and survived another acute attack of myocardial infarction, and twenty-eight have been treated for definite congestive failure.

The most prominent symptom after discharge from the Army has been dyspnea on exertion. This symptom was present in 208 (62 per cent) of the 334 patients for whom detailed records were available. Twenty of these men have experienced attacks of orthopnea and six have had attacks of nocturnal dyspnea, but only ten have had dyspnea continuously at rest.

The next most prominent symptom has been angina of effort, which was present in 175 (52 per cent) of the 334 cases. Two hundred twenty-seven men

gave no history of angina of effort before the attack, and 137 of this group have had these symptoms since the attack. Data were available in fifty-seven of the seventy-three patients with angina of effort before the attack; in thirty-eight of these the angina has persisted, while in nineteen there has been no angina since the attack.

In thirty-one additional patients in whom there was no angina of effort before the attack there have since been episodes of thoracic pain which were usually of short duration and in no way associated with exertion. In four other patients there has been a vague history of thoracic pain not associated with exertion; this symptom occurred in patients who had had the anginal symptoms prior to the attack.

A prominent symptom experienced by sixty-five of the 334 men has been a feeling of tiredness, described by such phrases as "easily fatigued," "no pep," "tired out with exertion," and "tired feeling all the time." Weakness was present in twenty-seven patients. Palpitation was noted in forty-two patients and was described by the phrases, "can feel the heart beat" (fifteen patients), "heart palpitates" (twelve patients), "heart jumps" (ten patients), and "heart pounds" (five patients). A number of patients (thirty) have become extremely nervous, apprehensive, and frightened since the attack. Nervous symptoms were reported as dizziness (twenty-five patients), headache (fifteen patients), fainting spells (eleven patients), insomnia (five patients), and hemiplegia (one patient).

Other symptoms noted since the attack have been cough (nine patients), choking attacks (six patients), tingling and numbness of the arms and hands (six patients), smothering attacks (four patients), tingling and numbness of the arms and legs (three patients), and indigestion (three patients).

Reports of physical examinations since discharge from the Army have been available in 342 cases, in 221 of which they were regarded as normal and in the other 121 as abnormal. Enlargement of the heart was noted in forty-eight of the latter, and this observation was verified by roentgenographic examination. Heart sounds were described as faint, distant, of poor quality, or barely audible in fifty-three patients. There were clinical signs of congestive failure in twenty-eight patients, in twelve of whom there was pitting edema of the feet and ankles; in five there was pulmonary congestion, and in eleven, the signs of more advanced congestive failure such as pulmonary râles, enlarged, tender liver, and edema of the lower extremities. In twenty-two patients systolic murmurs were detected, in twenty over the mitral area, in one over the aortic area, and in one along the left border of the sternum. In no instance was the murmur considered representative of an organic valvular lesion. Cyanosis was described in twenty-one patients. Premature contractions were noted in eighteen patients; sinus tachycardia with a rate over 100 per minute was recorded in twenty-one; gallop rhythm was heard in five; and pulsus alternans was detected in two patients.

In summary, in 248 cases the condition of the men has been regarded as stationary, in ninety-four as improved, in twelve as one of early improvement followed by relapse, and in forty-six as progressive, with increase in degree of impairment.

A statement as to the industrial history of 361 veterans since discharge from the Army is available. Of this group, 181 (50 per cent) have returned to full-time employment, and eighteen (5 per cent) are employed part-time. Twenty men (5 per cent) attempted to work but had to stop because of their physical condition, and 127 (36 per cent) have not been employed at any time. Fifteen veterans (4 per cent) have been attending school under the vocational rehabilitation training program of the Veterans Administration.

NEGRO PATIENTS

Because of the apparent dearth of information concerning coronary artery disease in Negroes, it was considered advisable to give the data separately for these patients. In our series there was a total of sixty-three Negroes, of whom twenty-six died and thirty-seven survived. The fatality rate among the Negroes was 41 per cent as compared with a rate of 55 per cent for the 803 white men.

Fatal Cases of Negroes.—Twenty-six Negroes under 40 years of age died of coronary artery disease during service in the Army. The age distribution of this group is as follows:

AGE IN YEARS	NUMBER OF CASES
21	1
23	1
26	2
28	1
29	1
30	2
31	2
32	4
33	2
34	3
35	2
36	1
38	2
39	2

The average age of this group at the time of the "attack" was 31.9 years, as compared with 32.4 years for the group of Negroes who survived the attack of coronary artery disease during military service.

Only six of the twenty-six men gave a past history of previous symptoms attributable to heart disease. The past clinical features in these six cases were as follows: one patient had had an attack three months before the final attack, one had experienced dyspnea on severe exertion, one had noted epigastric distress at times, one had had attacks of palpitation with precordial pain during the preceding six months, one had had a spell of syncope two months before the actual attack, and a sixth had experienced pains in the legs one month before the actual "coronary attack."

The most striking clinical feature of this group of Negroes who died in the Army was the large number who did not experience pain as a symptom of the "coronary attack." Only fourteen men (54 per cent) gave a history of pain,

whereas in twelve patients there is no record of any pain (in one of these the existence of pain would be better listed as "unknown"). On the other hand, among the group of Negroes who survived the attack thirty-four (92 per cent) of the thirty-seven men experienced pain as the outstanding clinical feature.

Among the fourteen men who experienced pain, this pain was localized over the precordium in seven instances, in the sternal region in two, in the epigastrium in two, in the upper back and epigastrium in one, in the right lower quadrant in one, and in the anterior chest region in one. Radiation of the pain was an uncommon clinical feature and occurred in only two instances, once from the sternum to the left arm and in another patient, from the epigastrium to the upper back.

Among the Negroes who survived the coronary attack, radiation of the pain was not a very common clinical feature, occurring in ten of thirty-four patients who had pain.

Other symptoms which accompanied the acute attack among the Negroes who died during Army service were dyspnea, nausea and vomiting, and congestive heart failure, to mention the most common. Dyspnea was present in four patients, vomiting alone in four, nausea and vomiting in two, nausea alone in one, and congestive heart failure in three patients. Other findings occurring only once each were rapid pulse, gasping, weakness, pallor, constipation, "gas," convulsions, and unconsciousness.

Among the men who survived there was a much higher percentage with a past history of probable heart disease, and a considerable number of them had experienced rather typical anginal symptoms before the onset of the actual attack, whereas in the group of patients who died there was only one man with a possible anginoid history. Over 90 per cent of the men who survived experienced pain during the "acute attack," whereas only 53 per cent of those who died are known to have had pain. However, some of the men who died suddenly may not have been questioned or were too ill to give a history.

The duration of illness in the twenty-six men who died was as follows: three had a sudden collapse, eight survived from a few minutes to one-half hour after the onset of the attack, six lived from one-half to four hours, three lived from four to twelve hours, and six lived longer than twenty-four hours: ten days, fourteen days, thirty-six days, seven months, eight months, and eight months, respectively.

Pathology.—For the twenty-six Negroes who died, the pathologic data related to the heart may be summarized as follows: Simple narrowing of the coronary arteries was present in six patients, and in one of these there was an infarct in the left ventricle. Sclerotic occlusion of a main coronary artery was present in five patients; the right coronary artery was involved in one instance, and the left anterior descending coronary artery was involved in four. Fresh thrombotic occlusion was present in ten cases. These thrombi involved the left anterior descending artery in eight patients, one of whom showed an organizing infarct in the anterior wall of the heart; another, an infarct in the left auricle with practically complete sclerotic occlusion of all the larger arteries, and a third, practically

complete sclerotic occlusion of all main arteries. In two patients the fresh thrombotic occlusion involved the right coronary artery.

Thrombosis featured two other cases. In one patient the lesion was described as a thrombus in the right coronary artery with a large infarct of the left ventricle, and in the other, as an organizing thrombus of the left anterior descending coronary artery.

In addition, there were two patients in whom there was an old thrombus in the left anterior descending artery with an old anterior infarct, and one with an old thrombus in the right coronary artery.

Surviving Negroes.—The age distribution of the thirty-seven Negroes who survived was as follows:

AGE IN YEARS	NUMBER OF CASES
20	1
21	1
27	2
28	3
30	4
31	3
32	3
33	4
34	2
35	3
36	4
37	3
38	4

Average age: 32.4 years

The height-weight relationship of the Negro group was similar to the entire group. Fifteen subjects (41 per cent) were below the normal standard, four being much below normal and eleven, moderately below normal. Eight subjects (26 per cent) were in the normal range, while fourteen (38 per cent) were above the normal range. Nine of these latter men were moderately above normal and five were much above normal.

The history relative to the previous existence of heart disease revealed the same trend as among the entire 400 survivors. Seventeen had no previous history of heart disease. Sixteen (43 per cent) presented histories of some cardiovascular disorder; ten had histories rather typical of the anginal syndrome, three were known to have had a previously existing hypertension, and three had had a previous diagnosis of definite organic heart disease. Four other patients gave a history that was suggestive of heart disease.

Only seven Negroes gave a history of some cardiovascular disturbance in the immediate family; the other thirty men in the group had no knowledge of any family history of heart disease. The family history of the seven men in whom it was significant could be listed as follows: one brother with "heart disease"; two mothers living with high blood pressure; two fathers dead of cardiac decompensation; one mother dead of "heart disease"; and one mother living with "heart disease." Thus, the incidence of known heart disease was much lower

among the Negro patients than among the white patients in this series. Among the surviving Negroes a knowledge of heart disease in the immediate family was admitted by only seven (11 per cent), whereas among the surviving white patients, 163 of 363 (43 per cent) gave a definite history of heart disease in the immediate family. This difference in family history between the two groups may be due to the difficulties in obtaining accurate histories from the Negro patients.

All of the Negroes included in this study presented clinical evidence, supported by electrocardiographic data and other laboratory findings, to support the final Army diagnosis of myocardial infarction. In twenty-one the onset was sudden and dramatic; in six a typical anginal syndrome had existed for at least six weeks preceding the attack of myocardial infarction; in five there was a history of long-standing, somewhat vague symptoms; and in five, symptoms suggestive of a "prodromal" attack occurred five to fifteen days before the acute episode.

As with the entire group of men included in this study, pain was the outstanding clinical symptom. Thirty-four of the thirty-seven Negro survivors experienced pain as the primary and most important symptom accompanying the onset of the attack of myocardial infarction. The pain was located as substernal in eleven cases, precordial in eight, left chest in six, epigastric in five, and in the chest without more definite localization in four.

The pain was localized in twenty-four instances and radiated to various parts of the body in ten others. The pain radiated to the left shoulder in three patients, to the left arm in two, to the substernal area in two, to the left axilla in one, between the shoulders in one, and to the left scapula and upward into the neck in one.

The initial pain was aggravated by respiration in four patients (10.8 per cent); this corresponds closely with the thirty-seven instances of this clinical finding among 363 white patients.

In the three patients without pain, the initial symptoms were palpitation caused by runs of premature ventricular contractions in one and dizziness in two. In all three the onset of the attack was also accompanied by dyspnea.

Other symptoms that were present during the "acute attack" and followed the initial symptoms were: dyspnea in eighteen patients, weakness in seven, sweating in five, vomiting in three, loss of consciousness in three, palpitation in two, and dizziness in two; semiconsciousness, anorexia, diarrhea, headache, warm feeling over the body, smothering sensation, and numbness of the extremities were each described once.

Blood pressure readings were obtained in the majority of patients at the time of induction into the Army and during the "acute attack." In only one patient was the blood pressure reading not recorded during the "acute attack" or at the time of induction, and in one other patient the record during the "acute attack" was not available. In the remaining thirty-five patients the induction blood pressures were normal in twenty-eight, slightly elevated in three, and not recorded in four. During the "acute attack" the first blood pressure taken during the initial physical examination was normal in eighteen, slightly elevated

in seven, moderately elevated (150/120) in one, low in five, and not taken in four patients.

In the seven patients in whom the blood pressure was slightly elevated during the "acute attack" the induction blood pressures were normal in five and slightly elevated in one, and in one the induction blood pressure was not recorded. In the one patient in whom the blood pressure was moderately elevated during the "acute attack" the induction blood pressure was normal.

A review of the records of the physical examinations revealed findings similar to those in the entire series. In nineteen patients, the physical examinations were entirely within normal limits. Arrhythmias were the most common deviation from the normal. There were four patients with premature ventricular contractions, four with sinus bradycardia (rates between 50 to 60), one with transient auricular fibrillation, and one with sinus tachycardia.

The heart sounds were described as faint or of poor quality in three patients; gallop rhythm was present in two; transient, nontransmitted apical systolic murmurs were present in three; and an accentuated, tambourlike aortic second sound was heard in one patient. Pericardial friction rubs were heard in two patients at the initial examination and in another case on the third hospital day. Pulmonary edema was considered to be present in three individuals. Frank, clinical shock with pallor, cyanosis, and sweating was present in one patient. The only sign of aging noted on the physical examinations was arcus senilis in two patients.

The diagnosis of arteriosclerotic heart disease as coronary occlusion, thrombosis, or myocardial infarction was made initially in twenty-one (57 per cent). Among the white patients the first clinical impression was listed as coronary arteriosclerotic heart disease in 283 (71 per cent). In thirteen patients the first diagnoses differed from the final clinical diagnosis of myocardial infarction. In three patients the diagnosis was deferred without any recorded evidence that possible coronary artery disease actually existed.

The following is a list of the first clinical impressions which were later considered incorrect: essential hypertension was recorded in two patients; and functional heart disease, psychoneurosis, pleurisy, intercostal neuralgia, chronic bronchitis, penetrating duodenal ulcer, perforated peptic ulcer, hiatus hernia, "eventration of the stomach into the lungs," gastric ulcer, and gastroenteritis were each recorded in one patient.

Electrocardiograms were available in all of the thirty-nine Negro patients. In thirty-two the records revealed classical localizing features of myocardial infarction. In fifteen the records were characteristic of anterior infarction, in fourteen, of posterior infarction, in two, of posterolateral involvement, and in one, of lateral infarction. In five patients there was not sufficient evidence to localize the lesion definitely, and in these the electrocardiograms were interpreted as representing myocardial damage.

From the data concerning the sixty-three Negroes in one series it is obvious that we cannot agree with Hunter[97] that the symptomatology of coronary artery occlusion in Negroes is different from that in Caucasians, at least in men under 40 years of age. None of Hunter's sixteen Negro patients had pain, whereas

all had congestive failure of long standing, and the acute coronary artery occlusion was heralded by an exacerbation of the symptoms of the congestive failure. It is evident that Hunter was dealing with an entirely different category of patients, and undoubtedly an older group. Apparently Negroes with acute coronary artery occlusion are rarely hospitalized in civil life, if one is to judge from the literature.

SIXTEEN ADDITIONAL CASES IN WHICH DEATH OCCURRED

In addition to the 850 cases thus far described there were sixteen in which death occurred but which were not adequately examined by us from the standpoint of the pathologic anatomy. The clinical records of these cases were adequate and were thoroughly reviewed. All of the patients were discharged from the Army because of myocardial infarction. A summary of the clinical features of these sixteen cases follows:

AGE IN YEARS	NUMBER OF CASES
23	1
30	1
33	1
34	1
35	2
36	1
37	3
38	2
39	4

Nothing was apparent in the clinical course or follow-up studies that was remarkably different from the same features in the 400 cases of nonfatal myocardial infarction.

Twelve of the sixteen patients gave no previous history of any cardiovascular disease, two had experienced definite anginoid attacks for three to six months previous to the actual acute episode, and two were known to have had a relatively severe arterial hypertension for several years.

The clinical picture of the acute attack of myocardial infarction was sufficiently typical to lead the clinicians to diagnose the nature of the disease correctly in fourteen of the sixteen patients. In the other two patients the diagnoses were congestive heart failure of undetermined cause and possible rheumatic heart disease.

The onset of the "acute attack" of myocardial infarction was sudden and without any previous warning in twelve cases; in three patients the onset was gradual over periods of one to six months, and in two of these three cases the men previously had had rather typical attacks of angina of effort. One patient did not experience definite pain at any time during the clinical course, and the symptoms started with weakness and shortness of breath followed by frank congestive heart failure.

Pain was the outstanding clinical symptom and was present in fifteen of the sixteen patients, being the primary symptom in eleven, whereas in two patients the primary symptom was a feeling of tiredness, and in one it was sudden marked

dyspnea. The pain was classical in all instances. The initial pain radiated in eleven instances; the distribution of this radiation was to both arms in five, to left shoulder and arms in three, and to left chest, neck, and right arm, and to left arm and neck in one patient each. In four patients there was no radiation of the pain.

Reports of complete physical examinations made during the initial attack were available in all sixteen cases. The cardiac examination in nine patients was reported as entirely normal; transient systolic apical murmurs were heard in three, and transient gallop rhythm and premature ventricular contractions were each noted in two patients. Tachycardia of moderate degree was noted in three patients, and bradycardia was observed in one.

Pulmonary congestion was detected in three patients, in one of whom there was congestive heart failure. One patient was in severe shock with the accompanying pallor, cyanosis, and cold, clammy skin.

Roentgenograms of the chest were available for all patients of this group. In eleven patients the heart was considered to be of normal size and shape. In five patients the heart was reported to be enlarged, in three of whom the enlargement was reported as marked, and in one patient a large ventricular aneurysm was later noted during the period of hospitalization.

Electrocardiograms revealed classical changes of acute myocardial infarction in all but one patient. The electrocardiographic pattern was classical for anterior infarction in seven patients, typical of posterior infarction in six, diagnostic of posterolateral infarction in one and of anteroposterior infarction in one, and indicative of myocardial damage in one.

Analysis of the blood pressures made during the acute attack of myocardial infarction showed a drop below normal standards in two patients; in six the pressures remained within normal range, in four the pressures were definitely elevated, and in four no blood pressure records were available. The induction blood pressures were normal in nine patients, definitely elevated in four, and not recorded in two. All of the elevated blood pressure readings noted during the acute attack occurred in men with normal induction blood pressure readings. In the four patients with elevated blood pressures at the time of induction the blood pressures were in the normal range in two during the acute attack, and in the other two, pressures were not recorded during the acute attack.

Temperature readings were available in twelve patients during the acute attack, and in all but one there was a definite elevation of temperature. The highest levels reached were 99 to 99.1° F. in four patients, 100 to 100.9° F. in one, 101 to 101.9° F. in two, and 102° F. or higher in four. In every case the temperature dropped to within normal limits no later than nine days after the onset of the acute attack.

Other available clinical data include sedimentation rates and white blood counts in fourteen of the cases. The sedimentation rate was normal in three patients, slightly elevated in one, moderately elevated in five, and markedly elevated in six. The leucocyte count was normal in two patients, slightly increased in two, moderately increased in nine, and greatly increased in one.

The clinical course in these sixteen cases was described as uneventful in seven patients, and as "stormy" and/or as having additional complications in nine. Congestive heart failure necessitated prolonged hospitalization for two patients; pulmonary infarction occurred in two, probable recurrent myocardial infarct in one, and frequent recurrent episodes of substernal pain with the slightest activity in two.

All of the patients were discharged as ambulant from the Army hospitals into civilian life. Because of their physical condition, none of these patients tried to gain employment. From the time of the first symptoms attributed to an acute attack of myocardial infarction the duration of life of patients in this group ranged from one and one-half months to thirty-two months. Four lived one and one-half to six months after the initial attack, seven lived between six and twelve months, two between one and two years, and three between twenty-four and thirty-two months. Seven patients died at home; there are no records available for four of these patients, and three members of this small group died suddenly and unexpectedly. There was no post-mortem information available for these seven patients. The remaining nine patients were hospitalized subsequent to their discharge from the Army hospital, eight in Veterans Administration hospitals and one in a private hospital. Recurrent myocardial infarction was responsible for the death of four of these patients and chronic congestive heart failure, in addition to the myocardial infarction, caused the death of three. Chronic congestive heart failure was responsible for two other deaths. Multiple pulmonary infarction was considered the cause of the death of another patient. One patient died suddenly with acute pulmonary edema after an acute illness of only ten hours. Another patient died shortly after the onset of hemiplegia and unconsciousness that were attributed to cerebral embolization. There were five autopsies performed in this group of patients, all confirming the diagnosis of previous myocardial infarction.

ILLUSTRATIVE CASES AMONG THE SURVIVORS

CASE 190 (Typical Anterior Myocardial Infarction).—A 28-year-old infantryman, whose former occupation was that of a painter, was inducted into the Army Jan. 20. 1943. His blood pressure then was 118/80, his height, 64.5 inches, and his weight, 141 pounds. His family history was irrelevant except possibly for the fact that his mother had bronchial asthma. The patient had used alcohol and tobacco moderately. In 1938 he had had an attack of pain in his precordium radiating down his left arm. On June 14, 1944, after climbing a steep hill, he had an attack of severe pain in the left thoracic region anteriorly, radiating down the left arm, which became numb. He vomited, became very short of breath, and was apprehensive. He entered the hospital the same day.

On admission he had an anxious expression, was writhing in pain, and was clutching his left chest. He was coughing and dyspneic and cyanotic. His heart was normal on examination. His pulse rate was 110 per minute and his blood pressure, 140/95. Later the same day the blood pressure was 144/108, and the following day it was 105/70, after which it remained at a normal level. The temperature rose from 97 to 101°F. and returned to normal by lysis after five days. The dyspnea and cyanosis gradually improved after the administration of oxygen, morphine, and bed rest. He was then asymptomatic after recovering from the acute phase of the "attack."

The white blood cell count was 17,700 with 78 per cent polymorphonuclear leucocytes on June 15; 11,500 with 86 per cent on June 20; and 8,950 with 48 per cent on June 26. Sedimentation rates were 8 mm. in one hour on June 20, 23 mm. on June 26, 10 mm. on July 1, 9 mm. on July 1,

9 mm. on July 29, and normal thereafter. The electrocardiograms went through the progressive changes of acute anterior myocardial infarction during the first thirteen weeks, as shown in Fig. 1. Roentgenograms of the chest made on June 25 and September 11 were normal.

The soldier was discharged from the Army on Nov. 1, 1944, with the diagnosis of arteriosclerotic heart disease and thrombosis of the anterior descending coronary artery. He resumed his work as a painter.

Nine months after discharge the veteran was examined by physicians of the Veterans Administration. In the interval he had had symptoms of shortness of breath and precordial pain on exertion, with edema of the feet and ankles. Physical examination revealed the heart to be of normal size and a faint systolic murmur at the mitral area. The heart sounds were of normal quality, except that the aortic second sound was accentuated. The diagnosis was coronary artery sclerosis with the anginal syndrome.

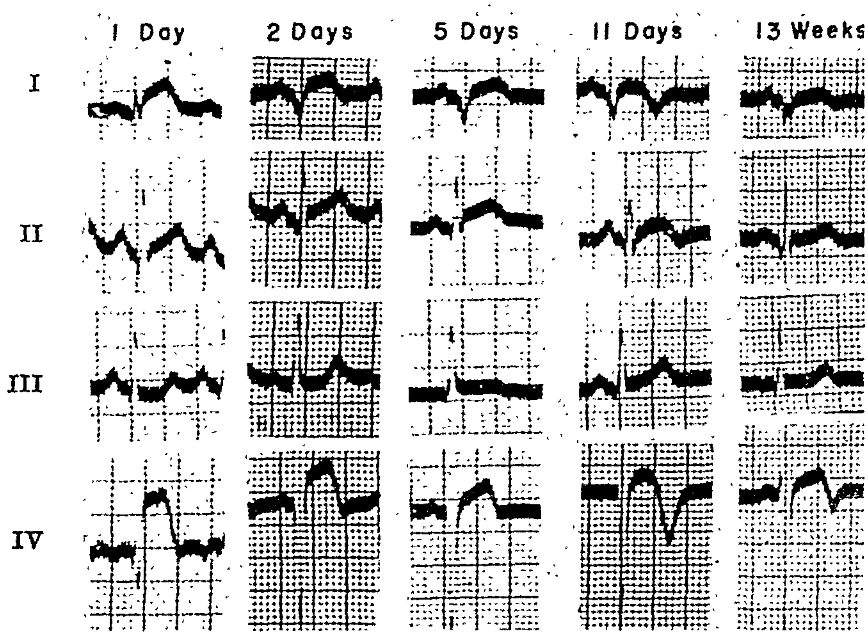

Fig. 1.—Case 190. Survivor, 28 years of age. Typical anterior myocardial infarction.

Case 92 (Typical Posterior Myocardial Infarction).—A 25-year-old white infantry staff sergeant, whose former occupation was that of a laborer in a brass foundry, was inducted into the Army Oct. 12, 1941. At that time his blood pressure was "normal," his height, 67 inches, and his weight, 170 pounds. His family history was irrelevant, and his past history was negative for cardiovascular disease. He smoked moderately and denied the use of alcohol.

On April 3, 1943, while checking supplies, the sergeant suddenly experienced a squeezing, viselike, retrosternal pain which radiated to both shoulders and down the arms to the fingers. He began to sweat and to have hot and cold sensations; he could neither get into a comfortable position nor catch his breath. He went to the dispensary and was relieved in five minutes by a hypodermic injection, but after forty-five minutes the symptoms returned. About six hours after the onset of symptoms the patient was hospitalized.

On admission the soldier appeared to be acutely ill, was restless, cold, clammy, perspiring, and of ashen color. The right pupil was larger than the left. He was very dyspneic and complained of a severe, viselike pain in the sternal region. The heart sounds were of poor quality. The rhythm was irregular because of premature contractions. The blood pressure was 120/80, the plus rate was 50, and the temperature, 99.6° Fahrenheit. The clinical diagnosis was coronary artery disease.

The blood pressure was normal throughout the entire period of hospitalization. The temperature rapidly became elevated; on the second day it was 99.4° F., on the third day, 101° F.,

on the fifth day, 99.2° F., on the sixth day, 99° F., and the seventh day and thereafter, normal. During the first forty-eight hours morphine, oxygen, and absolute bed rest were prescribed. After the acute phase, the clinical course was asymptomatic.

The white blood cell counts were 10,600 with 75 per cent polymorphonuclear leucocytes on April 4, 9,600 with 82 per cent on April 5, and 5,900 on April 16. The sedimentation rate was 3 mm. in one hour on April 5, 16 mm. on April 18, 5 mm. on April 20, and 1 mm. on April 28. Electrocardiograms showed the progressive changes of acute posterior myocardial infarction, as shown in Fig. 2. A roentgenogram of the chest was normal.

The patient was discharged July 23, 1943, with the diagnosis of acute coronary artery occlusion. He was examined seven months, and again two years and four months, after discharge from the Army. He complained of shortness of breath and a "catching" sensation across the upper part of the chest. No abnormal physical signs were elicited. The blood pressure was 116/80 and the heart rate, 80 per minute. A roentgenogram of the chest showed the heart and aorta to be normal. The diagnosis was coronary arteriosclerotic heart disease with previous coronary artery thrombosis, posterior myocardial infarction, and myocardial insufficiency.

Since discharge the patient has been gainfully employed at moderately hard unskilled labor.

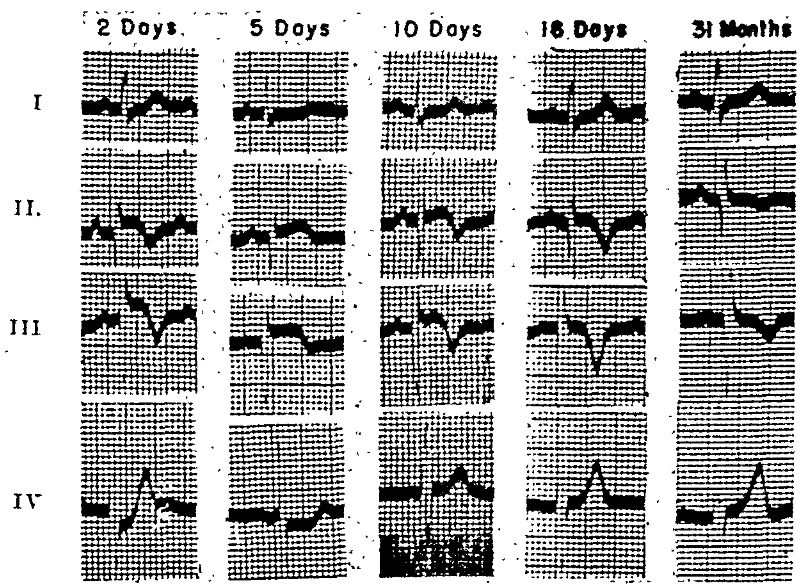

Fig. 2.—Case 92. Survivor, 25 years of age. Typical posterior myocardial infarction.

Case 71 (Posterior Myocardial Infarction With Minimal Symptoms).—A 35-year-old white private, who before induction had been operator of a rubber mixing machine, entered the service March 3, 1943. His blood pressure at that time was 144/90, his height, 65 inches, and his weight, 232 pounds. His father had died at the age of 62 of a "heart attack." The patient had had mild hypertension for at least two years before his attack. He used tobacco moderately and alcohol occasionally. He had been obese for years. Prior to admission he had always felt well. While lifting some boxes on June 3, 1943, he suddenly developed a mild substernal ache which lasted for about two minutes and was associated with a tingling sensation down both arms. After this, he felt perfectly well, but because this had been the first instance of a physical complaint since he entered the Army, he reported to the medical officer. The latter, knowing the soldier's record, hospitalized him at once.

His complexion was florid and he appeared well; he weighed 220 pounds. His blood pressure was 160/100, his pulse rate was 84 per minute, and his temperature, 98° Fahrenheit. The physical examination was negative. The clinical impression, however, was coronary thrombosis and essential hypertension.

The course was entirely asymptomatic, but the temperature reached 101° F. in forty-eight hours and returned to normal by lysis by the eighth hospital day. Moderate leucocytosis and increased sedimentation rates returned gradually to normal. The blood pressure on the second day was 150/120 and thereafter attained normal levels, with an occasional slight systolic or diastolic elevation. The white blood cell count was 14,800 with 81 per cent polymorphonuclear leucocytes on January 4, 11,050 with 74 per cent on January 8, and 8,200 with 72 per cent on January 11. The sedimentation rate was 19 mm. in one hour on January 4, 58 mm. on January 8, 15 mm. on January 15, 8 mm. on February 6, and 5 mm. on February 12. A series of electrocardiograms showed typical evidence of posterior myocardial infarction, as shown in Fig. 3. A roentgenogram showed some prominence of the left ventricle, the transverse diameter of the heart being 15.8 cm., with the transverse diameter of the thorax 33.5 centimeters. The soldier was discharged from the Army on March 16, 1945. The final diagnosis was posterior myocardial infarction, probably due to coronary artery sclerosis with occlusion.

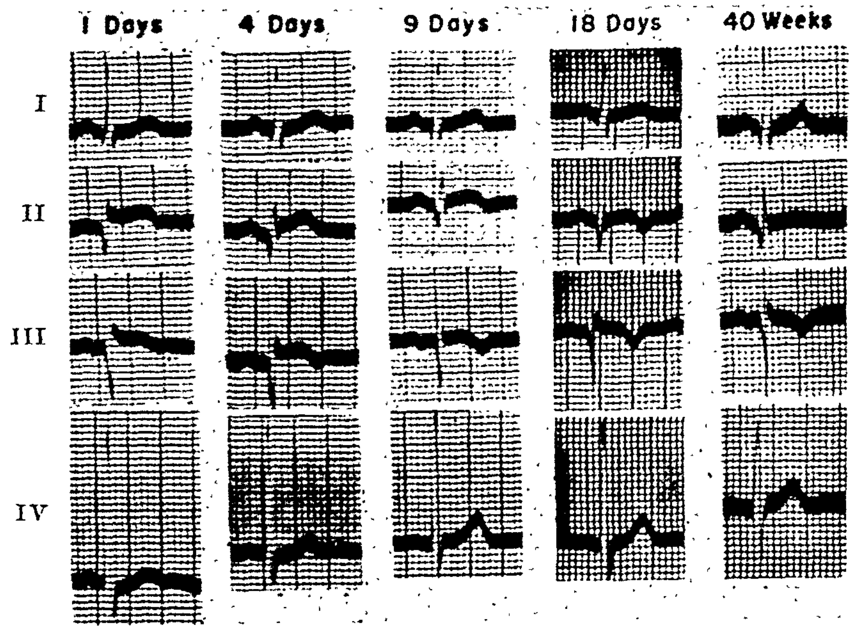

Fig. 3.—Case 71. Survivor, 35 years of age. Posterior myocardial infarction with minimal symptoms.

The veteran was examined on Sept. 13, 1945, six months after discharge from the Army. He had no complaints. His weight was 238 pounds. The blood pressure was 146/104 and the pulse rate, 96 per minute. The physical examination was negative. Roentgenogram of the chest showed the left border of the heart to be rounded, with a transverse diameter of 16.5 centimeters. The man had been working full time at the same job he had formerly held.

Case 327 (Prodromal Symptoms for Three Weeks).—A 30-year-old white staff sergeant, whose former occupation had been that of bus driver, had been inducted into the Army Oct. 7, 1941. His blood pressure then had not been recorded, but his height was 69.5 inches and his weight, 172 pounds. His father had died of "heart trouble and pneumonia." The patient's past history was irrelevant. He had used tobacco and alcohol moderately. On Feb. 21, 1944, he was admitted to the hospital, having complained for six days of a pressing pain in the anterior thoracic region radiating to the neck and both arms. There had been many attacks of short duration, six of which had lasted five minutes each, accompanied by profuse sweating, pallor, and palpitation. Severe attacks awakened the patient from sleep on three occasions and recurred once while he was walking, once while he was reading, and once while he was taking exercise. Between the attacks, many of which lasted less than a minute, he was comfortable. The entire physical examination was normal, the blood pressure being 130/80 and the pulse rate, 84 per minute. Coronary artery disease or paroxysmal auricular tachycardia was suspected.

The patient was kept at absolute bed rest because of recurring substernal pain lasting four to five minutes and accompanied by sweating. Serial electrocardiograms were made from the first to the eleventh day. These were normal except for minor variations (Fig. 4).

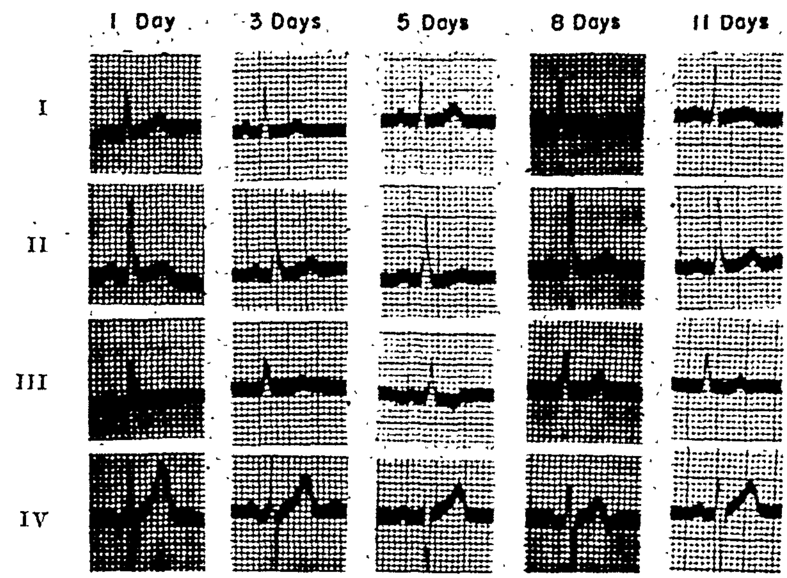

Fig. 4.—Case 327. Survivor, 30 years of age. Electrocardiographic series made during the three weeks of prodromal symptoms.

The course was afebrile and asymptomatic except for the intermittent pains until the seventeenth hospital day when a severe protracted pain developed, with dyspnea, sweating, and pallor. Within thirty-six hours the temperature rose to 101.2° F. and reached normal again by lysis after six days. The blood pressure immediately before the onset of this attack was 130/80; fifteen minutes after the onset it was 160/130; twenty-four hours later, 150/102; and forty-eight hours

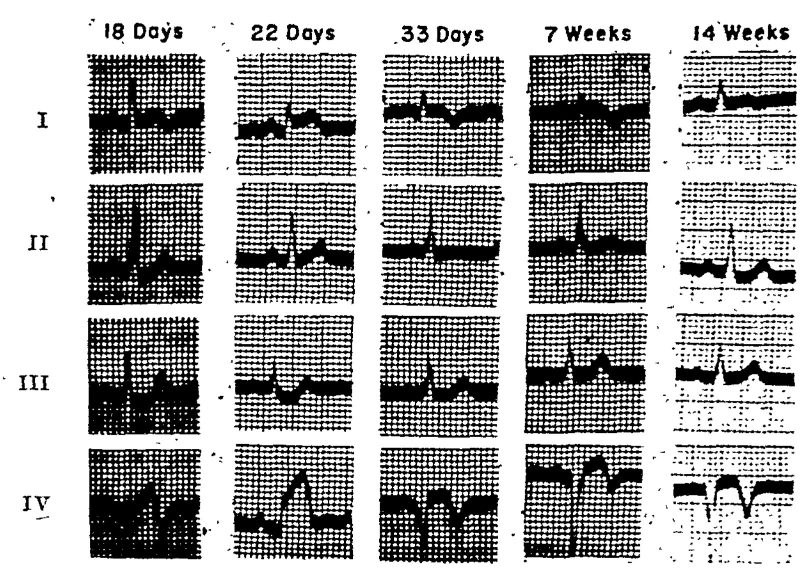

Fig. 5.—Case 327. Electrocardiographic series made during course of anterior myocardial infarction following three weeks of prodromal symptoms (compare with Fig. 4).

later, normal. Repeated white blood cell counts ranged from 8,900 to 6,500 with 68 to 64 per cent polymorphonuclear leucocytes. Many sedimentation rates ranged from 12 to 1 mm. in one hour. A roentgenogram of the chest was negative. A series of electrocardiograms now showed the progressive changes of acute anterior myocardial infarction (Fig. 5). The patient was discharged from the hospital on July 14, 1944, with the diagnosis of acute coronary artery thrombosis with anterior infarction.

The verteran was examined eight months after his discharge from the Army. He had had slight substernal pain and dyspnea on exertion. The physical examination was normal. The blood pressure was 134/92. A roentgenogram indicated that the heart was of normal size and shape. An electrocardiogram was similar to a tracing made during the fourteenth week after the main attack. Since September, 1944, two months after discharge, the veteran had been gainfully employed as inspector of motor vehicle equipment.

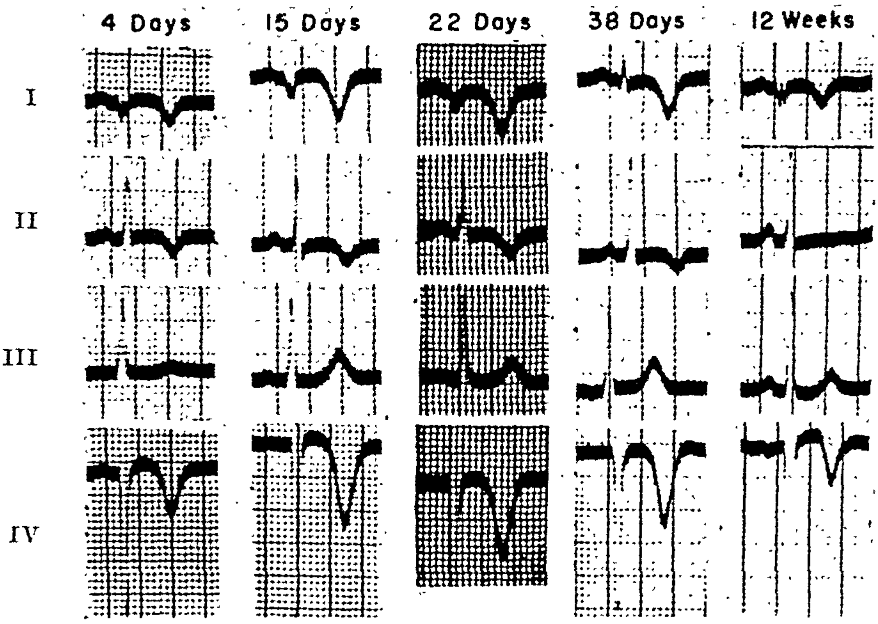

Fig. 6.—Case 34. Survivor, 28 years of age. Anterior myocardial infarction in a Negro.

CASE 34 (Acute Anterior Myocardial Infarction in a Negro).—A 28-year-old Negro corporal of the Army Air Force, whose former occupation was that of a hospital attendant, had been inducted into the Army Aug. 3, 1942. His blood pressure then was 108/68, his height, 65 inches, and his weight, 173 pounds. His mother, living, had high blood pressure. His previous history was irrelevant. He used tobacco and alcohol moderately.

The corporal felt well until two days before admission to the hospital, when pain suddenly developed in the left pectoral region and substernal area. On deep breathing, the pain radiated to the neck and left shoulder. It was, at first, "more of an ache than a pain," but it gradually became more severe and agonizing, and marked dyspnea ensued.

On admission, Jan. 30, 1944, he was observed to be very dyspneic and apprehensive and he complained of excruciating pain in the precordium. The heart appeared to be normal, with an occasional premature beat; otherwise the examination was negative. The blood pressure was 135/100, the pulse rate, 96 per minute, and the temperature, 97° Fahrenheit. The clinical impression was that of pleurisy on the left side, but heart disease was to be ruled out.

Shortly after admission the patient vomited. The temperature rose gradually to 102° F. on the third hospital day and three days later declined to normal, where it remained. A transient pericardial friction rub was heard on the fourth and fifth hospital days. After the first day all blood pressure readings were within normal limits. Convalescence was uneventful. The white blood cell counts were 19,000 with 84 per cent polymorphonuclear leucocytes on January 31 and 10,000 with 66 per cent on February 4. The sedimentation rate was 11 mm. on February 4, 8 mm.

on February 14, 11 mm. on February 15, and 4 mm. on two later dates. A series of electrocardiograms gave evidence of acute anterior myocardial infarction, as shown in Fig. 6. Report of a roentgenogram of the chest on February 4 stated, "The heart appears enlarged, with the cardiothoracic ratio well over 50 per cent, and generalized increase in the lung markings throughout." On February 11, report of another film noted: "The heart appears enlarged; it has a hypertensive configuration." The soldier was discharged from the Army on April 20, 1944, with the diagnosis of (1) thrombosis of a coronary artery due to coronary arteriosclerosis and (2) myocarditis, degenerative, chronic, severe, due to the coronary artery disease and preceding thrombosis.

An examination two months after discharge from the Army revealed nothing abnormal, and there had been no symptoms. A roentgenogram of the chest revealed the cardiothoracic ratio to be 52.4. The veteran had completed vocational training as a barber and was planning to open his own shop.

(To be concluded in the November issue. The references will accompany the last section.)

THE EFFECT OF INTRAVENOUS AMINOPHYLLINE ON THE CAPACITY FOR EFFORT WITHOUT PAIN IN PATIENTS WITH ANGINA OF EFFORT

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THE use of aminophylline for the relief of pain due to coronary insufficiency has been the subject of considerable investigation. The pharmacologic evidence that aminophylline is a coronary vasodilator is quite conclusive, but opinion has been divided on its efficacy as a therapeutic measure for the relief of angina pectoris. In 1933, Wayne and Laplace[1] reported that euphyllin (aminophylline) administered intravenously to four patients with the anginal syndrome brought about improvement in only two of them, and that nitroglycerin had a much greater effect. They concluded: "Whatever, therefore, the effect of euphyllin in animal experiments, its action as a coronary dilator is insufficient to recommend its use in angina of effort." In 1937, Gold and coworkers[2] conducted an extended clinical trial of theophylline and aminophylline by mouth in the treatment of cardiac pain, using careful control measures and the "blind" technique. They reported that "patients with cardiac pain are unable to distinguish the effects of a placebo from those of a xanthine when measures are taken to preclude the identification of the agent by any means other than the relief of pain. It is concluded that the xanthines exert no specific action which is useful in the routine treatment of cardiac pain." In 1939, Master and associates[3] reported that oral aminophylline produced improvement in 31 per cent of 127 cases of anginal syndrome and diminished pain 50 per cent of the times it was used. However, since they obtained almost identical results with milk sugar (30 per cent and 52 per cent, respectively), they stated: "obviously one cannot ascribe a specific effect to a drug when its action is no better than that of an inert substance."

In contrast to these unfavorable reports, Brown and Riseman[4] reported in 1937 that of seventeen patients with angina pectoris who were given aminophylline by mouth, 59 per cent were benefited, 12 per cent showing increases of 50 to 100 per cent in exercise tolerance. Massel[5] reported in 1939 that of five patients given eight courses of treatment with aminophylline by mouth, four courses gave relief and four were ineffective. In 1940, Levy and co-workers[6]

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reported a study of the effects of drugs on the anginal syndrome induced by anoxemia and on the electrocardiogram during pain. In ten tests with intravenous aminophylline, they reported a prolongation of 63 per cent in the time of appearance of pain and a diminution of 58 per cent in the RS-T deviations. When aminophylline was given by mouth, it caused a prolongation of 26 per cent in the time of appearance of pain, and the RS-T deviations were diminished by 32 per cent. One year later, Williams and associates,[7] in a similar study, reported that seven patients given 3 grains of aminophylline three times a day, by mouth, showed no significant delay in the onset of pain (8 per cent) and an average diminution in RS-T deviations of 36 per cent. In a group of five patients given 0.48 Gm. of aminophylline intravenously, the onset of pain was delayed 75 per cent and the RS-T deviations were diminished by 49 per cent. In 1941, LeRoy[8] studied sixty-eight patients with angina pectoris and found that 75 per cent were improved by oral aminophylline. In the majority of the cases, the pain was on the basis of syphilitic coronary artery disease; the results are, therefore, not strictly applicable to the usual type of coronary arteriosclerosis.

Boyer,[9] discussing the status of therapeutic claims for aminophylline in 1943, stated that "the mere existence of honest differences in opinion suggests that these drugs may be without specific action in the treatment of cardiac pain." He placed "the burden of proof on those who claim therapeutic efficacy," and suggested that accepted statistical methods be employed to clarify the significance of clinical studies.

In view of these conflicting reports, and with the object in mind of establishing more clearly the status of aminophylline, it was decided to study the effect of the drug when administered intravenously, the test of exercise tolerance being used as the index, according to the method described by Wayne and Laplace.[1] In this method the patient exercises until he develops pain. The method differed from that employed by Riseman in that three successive trials were carried out on the same day, separated by rest periods of one hour, rather than one trial per day on successive days. The three tests were performed on the same day because, in contrast with Riseman, we found considerable variations in exercise tolerance in the same patient on different days. The rest period of one hour was chosen so as to eliminate the beneficial effect of exercise itself upon subsequent tests of exercise tolerance.[1]

All of the subjects were seen in the morning and each period of observation took from three to four hours. Preceding the test, the subject took no breakfast or medication. No sedation was taken the night before the test. Upon arrival, the patient rested for one hour in a comfortable easy chair, during which time frequent pulse and blood pressure determinations were made to provide an index of resting levels. The first test was then carried out by having the subject walk back and forth over a set of steps similar to those described by Master and Oppenheimer[10] until he developed anginal pain similar to his usual attacks in everyday activity. The average rate of walking per minute was determined, and in all subsequent tests on that patient the same rate of walking was maintained. A hinged step with a small mechanical counter attached was used to record the number of trips over the steps.

As soon as the onset of pain occurred, the subject sat down and rested for one hour. A second determination was then made, followed by another rest period of one hour and a third test. That completed the series of trials for any one patient on one day.

The study was conducted by the "blind" method. The materials for injection, 10 c.c. of a 2.4 per cent aminophylline solution and an identical quantity of physiologic saline, were prepared by a nurse, for each day, in identical syringes marked only with code numbers so that the contents were unknown to the observer as well as to the subject. A method was devised for varying the order of the trials (control test without any injection; control test with a placebo injection; and test with an injection of aminophylline) so that all possible combinations of the three tests were used in different sequence. The code numbers on the syringes indicated the order in which the injections were to be given. The contents of the syringes and the corresponding code numbers were noted on cards, sealed in envelopes, and kept sealed until the entire study was completed. Injections were given in a standard manner, starting at ten minutes before each exercise test, and continuing for five minutes (2.0 c.c. per minute); they were followed by five more minutes of rest before the exercise test was started. The first visit of each patient was devoted to control tests and occasionally to check the response to nitroglycerin.

The patients studied were selected from the active census of the cardiac clinic and were all unequivocal cases of arteriosclerotic or arteriosclerotic and hypertensive heart disease with chest pain brought on by exertion and relieved by rest and nitroglycerin. For the purpose of this study, it was decided not to include those patients in whom chest pain also occurred spontaneously at rest, thereby eliminating or minimizing the possibility of accidental end points not related to the exercise tolerance test. Patients receiving digitalis were also omitted because of the reported deleterious effect of digitalis on cardiac pain. Patients receiving diuretics, mercurial or otherwise, or manifesting evidence of cardiac failure were not included. Also excluded were patients who might not be able to perform the tests satisfactorily for other reasons, such as intermittent claudication, arthralgias, and marked obesity. The group that was finally selected provided us, therefore, with suitable indicators of the anginal syndrome, and the number of interfering factors was kept at a minimum.

RESULTS

In all, 124 tests were performed by a total of seventeen patients, but six patients were eliminated after preliminary testing because of failure to elicit an unequivocal end point or because of their inability to carry out the tests properly. In addition, certain tests were not included in the final data because of absence of pain end points in all trials on the day of testing or because of failure to complete the series of three tests on one day. The final data consisted of ninety-nine trials performed by eleven patients of which forty-six were trials without any injection, twenty-two were control trials with placebo injections, and twenty-two were trials following the intravenous injection of 0.24 Gm. of aminophylline. The remaining nine trials were used to check the response to nitroglycerin (Table I).

TABLE I. SUMMARY OF CLINICAL DATA AND RESULTS OF EXERCISE TOLERANCE TESTS

PATIENT	SEX	AGE	DIAGNOSIS	ECG	NUMBER OF TRIPS PERFORMED		
M. S.	M	46	Arteriorsclerosis, coronary sclerosis, old myocardial infarct	Myocardial damage	47(W) 52(W) 113(A)	33(W) 53(S) 65(W)	65(N) 120(A) 86(S)
C. S.	F	51	Arteriosclerosis and hypertension, enlarged heart, dilated aorta	Myocardial damage	15(W) 16(W)	16(W) 14(S)	15(N) 22(A)
H. M.	M	54	Arteriosclerosis and hypertension, coronary sclerosis, myocardial fibrosis	Normal	10(W) 26(A)	6(W) 27(S)	16(N) 29(W)
M. P.	M	52	Arteriosclerosis, old coronary thrombosis, myocardial fibrosis	Myocardial damage	81(W) 104(A) 65(S) 64(W)	96(W) 87(W) 102(A)* 86(S)	70(W) 94(S) 81(W) 102(A)*
M. R.	M	52	Arteriosclerosis and hypertension, enlarged heart, coronary sclerosis	Left ventricular strain	28(W) 26(S) 28(W) 35(A)	34(W) 42(A) 29(S) 35(W)	32(W) 39(W) 42(A) 31(S)
S. P.	M	53	Arteriosclerosis, enlarged heart, coronary sclerosis, myocardial fibrosis	Myocardial damage	7(W) 3(S) 8(W) 7(A)	7(W) 9(W) 13(A) 9(S)	13(N) 8(A) 11(S) 8(W)
S. Z.	M	41	Arteriosclerosis, coronary sclerosis, myocardial fibrosis	Myocardial damage	36(W) 64(A) 60(W) 60(S)	43(W) 80(W)* 61(S) 82(A)*	64(N)* 80(S)* 80(A)* 81(W)*

P. N.	M	64	Arteriosclerosis, old coronary thrombosis, dilated aorta	Myocardial damage	6(W) 11(S)	6(W) 6(A)	4(N) 6(W)
I. K.	M	59	Arteriosclerosis and hypertension, coronary sclerosis, diabetes mellitus		32(W) 24(W)	40(N) 38(A)	26(W) 34(S)
I. D.	M	61	Arteriosclerosis, enlarged heart, coronary sclerosis	Myocardial damage	24(W) 32(W) 42(A)	46(N) 54(A) 37(S)	29(W) 45(S) 43(W)
W. H.	M	56	Arteriosclerosis, enlarged heart, coronary sclerosis	Myocardial damage	9(W) 15(W) 29(A)	34(N) 32(A) 19(S)	15(W) 29(S) 23(W)

*No pain end point.
W = Control (walk, without injection).
S = Saline injection.
A = Aminophylline.
N = Nitroglycerine.

The first comparison of results was made with data obtained from tests in which the trials with saline preceded the trials with aminophylline (Table II). There were ten pairs of results in that sequence, and the differences in performance between the trials immediately following saline and the trials immediately following aminophylline were determined for each individual. The average of these individual differences was 19.8 trips, the standard error being ± 6.3 ($t = 3.14$; $p = 0.01$).

TABLE II. EXERCISE TOLERANCE WHEN TRIALS WITH SALINE PRECEDED TRIALS WITH AMINOPHYLLINE

PATIENT	NUMBER OF TRIPS		
	SALINE	AMINOPHYLLINE	DIFFERENCE
M. S.	53	120	67
C. S.	14	22	8
M. P.	65	102	37
	86	102	16
M. R.	26	42	16
	29	42	13
S. P.	3	8	5
S. Z.	61	80	19
	60	82	22
P. N.	11	6	−5
Average			19.8

A similar comparison was then made with the data obtained from tests in which the order was reversed, the trials with aminophylline preceding the trials with saline (Table III). There were twelve pairs of results in that sequence. The differences in performance were determined for each individual, and the

TABLE III. EXERCISE TOLERANCE WHEN TRIALS WITH AMINOPHYLLINE PRECEDED TRIALS WITH SALINE

PATIENT	NUMBER OF TRIPS		
	AMINOPHYLLINE	SALINE	DIFFERENCE
M. S.	113	86	−27
H. M.	26	27	1
M. P.	104	94	−10
M. R.	35	31	−4
S. P.	13	11	−2
	7	9	2
S. Z.	64	80	16
I. K.	38	34	−4
I. D.	54	45	−9
	42	37	−5
W. H.	32	29	−3
	29	19	−10
Average			−4.6

mean difference was found to be 4.6 trips more for aminophylline than for saline (standard error, ±2.9). Since t in this series is 1.6, this difference is not significant.

Whether saline injection alone produces any increase in the capacity for effort, through suggestion or other means, was not determined because the number of suitable tests for such a comparison was too small.

DISCUSSION

The literature on the effect of aminophylline on the capacity for effort without pain in patients with angina of effort is conflicting. While there seems to be little doubt that aminophylline is a coronary vasodilator, there is considerable doubt as to whether the usual oral doses are absorbed in sufficient concentration to prove of significant value in the treatment of the angina of effort. There seems also to be some doubt concerning the effectiveness of the coronary vasodilatation after intravenous injection, and it is in relation to this problem that the foregoing experiments were planned. In a series of experiments on patients with unequivocal angina of effort, so planned as to eliminate conflicting factors in the interpretation of the results, it was found that an intravenous injection of 0.24 Gm. of aminophylline increases the capacity to walk steps without pain. The statistical analyses of the data leave little doubt that the effect of aminophylline obtained in these experiments is a significant one. There were two sets of data, one in which the sequence of comparisons was saline-aminophylline, and the other in which the sequence was reversed, aminophylline-saline. It is of interest to note that the highly significant difference between saline and aminophylline which appeared in the first series of experiments was absent when the sequence was reversed, adding further weight to the observation that intravenous aminophylline exercises a specific effect in increasing the capacity for effort without pain, an effect which lasts longer than one hour since it was still present when the subsequent experiments with saline were performed.

The question of the practical significance of the foregoing observations is a matter of some interest; therefore, it is important to translate the statistical significance into practical terms. The increase of 19.8± the standard error of 6.3 trips, or 48± 16 per cent, over the performance with saline alone means that the chances that there is a real increase in performance are quite high, namely, about 99 out of 100. This does not, however, imply anything about the magnitude of the percentile increase. It may be anywhere from 1 to 96 per cent (mean ± three times the standard error). If we wish to attribute an actual value to the magnitude of this increase, the chances that we are correct in assigning such a value are not so high. For example, we can only be certain to the extent of about 95 out of 100 chances that the increase is at least 16 per cent (mean minus two times the standard error). And we can have practically no assurance, only about two chances out of three, that the increase is at least 32 per cent (mean minus one standard error). In other words, we are very certain that there is an increase in performance; we are fairly certain that the increase is about 16 per cent; we are not at all certain that the increase is any more than 16 per cent.

It should not be inferred, therefore, that the results obtained in these experiments justify the free use of aminophylline by oral administration or even by intravenous injection for the relief of effort angina. Nitroglycerin, taken sublingually, is a very effective method of obtaining coronary vasodilatation and increased capacity for effort without pain, and a tablet taken under the tongue is more convenient than an intravenous injection. The question remains as to which of these measures produces a greater effect and one of longer duration. This question is the subject of an investigation now under way.

SUMMARY

1. An intravenous injection of 0.24 Gm. aminophylline increases the capacity for effort without pain in patients with angina of effort. There are fairly marked individual variations in this response.

2. The increased capacity for effort without pain lasts longer than one hour.

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I. CORRELATION OF ELECTROCARDIOGRAPHIC AND PATHOLOGIC FINDINGS IN ANTEROSEPTAL INFARCTION

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THORACIC leads were utilized by Waller[1] in 1887 in connection with the capillary electrometer and were employed by Einthoven[2] prior to development of the string galvanometer. For more than twenty years after the application of the latter to clinical electrocardiography, it was standard practice to take merely the three limb leads recommended by Einthoven. During this period, however, direct epicardial and precordial leads were employed experimentally, notably by Lewis and co-workers in their studies of auricular flutter,[3] and by Wilson and associates in their studies of right and left ventricular potentials in normal animals[4] and in bundle branch block.[5] In 1930, Wilson[6] predicted the value of precordial leads in coronary occlusion and, with his associates, undertook a comprehensive study which extended over a period of several years.

Widespread clinical interest in precordial leads was awakened in 1932 by the report of Wolferth and Wood.[7] Their demonstration that certain anterior infarcts produced RS-T displacement in tracings taken through a precordial electrode, but not through extremity leads, has been amply confirmed. Following this report, it became customary in most clinics to supplement the three limb leads with a single precordial lead, usually applied in the vicinity of the apex, less commonly in the fourth intercostal space at the left sternal border, or at other sites. Nevertheless, the inadequacy of a single precordial lead, regardless of the point of application of the exploring electrode, has gradually become apparent, partly as a result of studies correlating electrocardiographic and pathologic findings. From the more extensive reports[8-12] a number of cases may be collected in which anterior infarction, not diagnosable from the four-lead electrocardiogram, was demonstrated at autopsy. On the other hand, patterns in Lead IV simulating those of anterior infarction were found in cases where the diagnosis was subsequently excluded at autopsy.[9,12]

Through a series of studies on dogs before and after coronary ligation, Wilson and associates[13-18] demonstrated the close correlation between the QRS-T pattern in multiple epicardial leads and the distribution of the infarct at autopsy. These studies form the basis for the utilization and interpretation of multiple

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precordial leads in human myocardial infarction and consequently will be briefly summarized.

In the characteristic lesion produced by ligation of a major coronary vessel, three concentric zones were distinguished pathologically: (1) a central zone of transmural infarction, extending through the entire wall from endocardium to epicardium; (2) a marginal zone of infarction confined to a portion of the wall, most commonly the subendocardial layer; and (3) an outlying zone of ischemia manifested by pallor and by absence of histologic evidence of degeneration. In smaller lesions, produced by ligation of secondary or tertiary branches, only the marginal and ischemic zones were represented.

The typical electrocardiographic pattern registered through direct epicardial leads from the central zone consisted of a QS complex with smooth descending and ascending limbs.[15] This QS deflection simulated the record obtained through an electrode inserted into the left ventricular cavity[13,14] and was attributed to transmission of cavity potentials to the surface through an infarct which, like a valvular orifice, behaved merely as a conducting window. The T wave in direct epicardial leads also resembled that recorded from the ventricular cavity when the intervening myocardium was completely destroyed.[17] On the other hand, a markedly elevated RS-T junction and monophasic upright T wave were obtained when the subepicardial muscle was acutely injured, but not dead. A notched rather than a smooth QS complex was the characteristic finding when a small portion of the underlying myocardium was spared.[15] The upstroke of the notch represented positive potentials momentarily referred to the epicardium as a result of activation of the remnant of responsive muscle.

The usual finding in epicardial leads from the marginal zone consisted of an abnormal QR complex,[16,17] which could be correlated with infarction of the subendocardial layer and preservation of the subepicardial layer of muscle. The initial Q represented negative cavity potentials transmitted to the surface during the time when the impulse traversed or circumvented the infarcted subendocardial muscle, and the succeeding R represented positive potentials referred to the surface as soon as the impulse reached and began to activate the intact subepicardial layer. An abnormally small initial R was recorded in direct leads when the infarct extended in patchy fashion through the underlying wall or when it was confined to the subepicardial layer.[16] The typical finding in epicardial leads over the ischemic zone consisted of a normal QRS and cove-shaped inversion of the T wave.[17] By means of multiple direct leads, it was thus possible to demarcate accurately the boundaries of an infarct and to gauge the thickness of the wall involved.

The major difference between the QRS-T contour in direct and that in precordial leads was referable to the fact that the tracing obtained through the latter was dominated by the potential variations of a much larger surface of epicardium than that obtained by the former.[18] In the presence of a large central zone of uniform transmural infarction, an overlying precordial lead revealed a QS complex comparable in shape to that obtained through direct leads from the subjacent epicardium. When the central zone was small, precordial leads tended to show a notched QS complex or a QR deflection due to

admixture of effects from the central and marginal zones.[16] While a sharp delineation between central, marginal, and ischemic zones could be made out in direct leads, a more gradual transition was found in precordial leads as a result of overlapping effects. Nevertheless, the data furnished by multiple precordial leads in experimental anterior infarcts in animals appeared to provide sufficiently accurate localization for clinical purposes.

The Wilson group introduced precordial leads V_1 through V_6 and unipolar extremity leads V_R, V_L, and V_F and have subsequently published detailed accounts[18,19] of the findings in these leads associated with infarcts in various locations. Their clinical deductions were confirmed in a few cases which came to autopsy. Kossmann and De La Chapelle[20] noted a close correspondence between the QRS-T pattern in the Wilson precordial and extremity leads and the findings at autopsy in a series of nine cases. Because of the very small number of reported cases with pathologic confirmation of the infarct diagnosed with the aid of multiple precordial leads, there appeared to be a need for an extensive study.

A correlative study of electrocardiographic and pathologic findings has been made in a total of 161 cases of myocardial infarction established at autopsy during a four-year period beginning in July, 1943. One or more electrocardiograms, consisting of precordial leads V_1, V_2, V_3, V_4, V_5, and V_6 and the standard limb leads, were obtained in every case, and the augmented unipolar limb leads were taken in 157 cases. All of our cases in which the foregoing twelve leads were available and in which myocardial infarction was definitely established and accurately localized at autopsy during the specified period are, with six exceptions, included in the series. These cases were omitted because the last electrocardiogram was taken some time before death and autopsy revealed merely a terminal infarct, which, from its pathologic characteristics, had unquestionably occurred after the last electrocardiogram had been obtained. Whenever there was doubt as to whether the electrocardiogram had been taken before or after the development of the infarct, the case was included in the series. A number of cases in which the precordial electrocardiogram was limited to Leads V_2, V_4, and V_6 were automatically excluded by this method of selection.

The method of clinical and pathologic study has been described in detail in a previous communication.[21] Post-mortem examination included injection of the coronary arteries with radiopaque mass, roentgenogram, and subsequent dissection with multiple transmural microscopic blocks in 152 of the 161 cases. The position of the infarct, as determined by inspection, was outlined on the roentgenogram with wax pencil and was corrected, when necessary, to conform with the microscopic findings. In some cases the infarct was delineated roentgenographically by its avascularity, but in many cases vessels within the infarct were filled with a radiopaque mass. In some of the latter, the vessels had undoubtedly carried blood prior to death, but in others, an ante-mortem thrombus may have been dislodged by forceful injection of the lead-agar mixture from a hand syringe. This did not detract from the objectives of the pathologic study, which were to determine the presence or absence of infarction,

to demarcate accurately the position of the myocardial lesion, and to estimate its age. No particular effort was made to trace the relation of the infarct to muscle bundles, as described by Robb and Robb[22] and by Lowe,[23] since in our experience the infarct usually involved more than one muscle bundle. The age of the infarct was determined from the criteria of Mallory and co-workers,[24] modified somewhat by our own experience.

In the presentation of our data, a detailed analysis has been made of the electrocardiogram of each individual case, independent of the pathologic findings, and subsequently an attempt has been made to correlate the findings in the various leads with those observed at autopsy. The anatomic location and age of the infarct have been described as briefly but as accurately as possible and illustrated, when necessary, by a reproduction of the roentgenogram. In order to save space, the pathologic criteria upon which the diagnosis of infarct was established and the age estimated are not included, but will be reserved as a subject for a separate communication. Furthermore, description of the pathologic findings pertaining to the coronary vessels is also omitted, since the electrocardiographic abnormalities are a direct manifestation of the secondary changes in the myocardium rather than the primary changes in the coronary arteries.

In spite of the foregoing curtailment, the data are too voluminous for condensation into a single manuscript. The cases have been classified into the following seven groups, according to the location of the infarct at autopsy, namely: anteroseptal, large anterolateral, anteroposterior, septal, posterior, posterolateral, and lateral. Considerable overlapping is unavoidable in any classification because of the frequency of two or more infarcts at autopsy and because of the tendency of large anterior infarcts to extend into the septum, the lateral wall, and around the tip of the ventricle to the posterior aspect of the apex, and the similar tendency of large posterior infarcts to extend into the septum and lateral wall. When the infarct could be classified anatomically into more than one category, the lesion of principal electrocardiographic interest became the determining factor.

Regardless of the category in which an individual case is classed, the discussion of the electrocardiographic-pathologic correlation covers all ramifications of the infarct.

In this communication, an analysis is presented of the electrocardiographic and pathologic findings in twenty cases of anteroseptal infarction. Wilson and associates[18,19,25] have utilized this term for electrocardiograms with diagnostic QRS abnormalities in one or more of the first four precordial leads, but not in V_5, V_6, or the standard leads. Our classification was based primarily on the autopsy findings. In the majority of our twenty cases, the infarct was limited to a relatively narrow strip of the free anterior wall of the left ventricle and the contiguous anterior portion of the interventricular septum and did not extend into the lateral or posterior aspect of the left ventricle. The remainder had a more extensive infarct or a multiple infarct, but were included because the lesion of principal electrocardiographic interest was in the anteroseptal wall of the left ventricle.

CASE REPORTS

CASE 1.—A woman, 49 years of age, was first hospitalized in August, 1943, for the control of diabetes mellitus complicated by hypertension. She was readmitted on Nov. 18, 1943, with a history of repeated vomiting for one week and with evidence of moist gangrene of both feet. She received a single dose of 20 units of regular insulin at 8:00 P. M. and three hours later was found in circulatory collapse with a blood pressure of 90/60. The infection was not controlled and death occurred in hyperpyrexia on November 21. No cardiac glycosides were given.

Electrocardiographic Findings.—Electrocardiograms obtained on November 19, twelve hours and eighteen hours after the onset of shock, are reproduced in Fig. 1 along with a record taken on the first admission. In the tracing of August 10, the abnormally late onset of the intrinsicoid

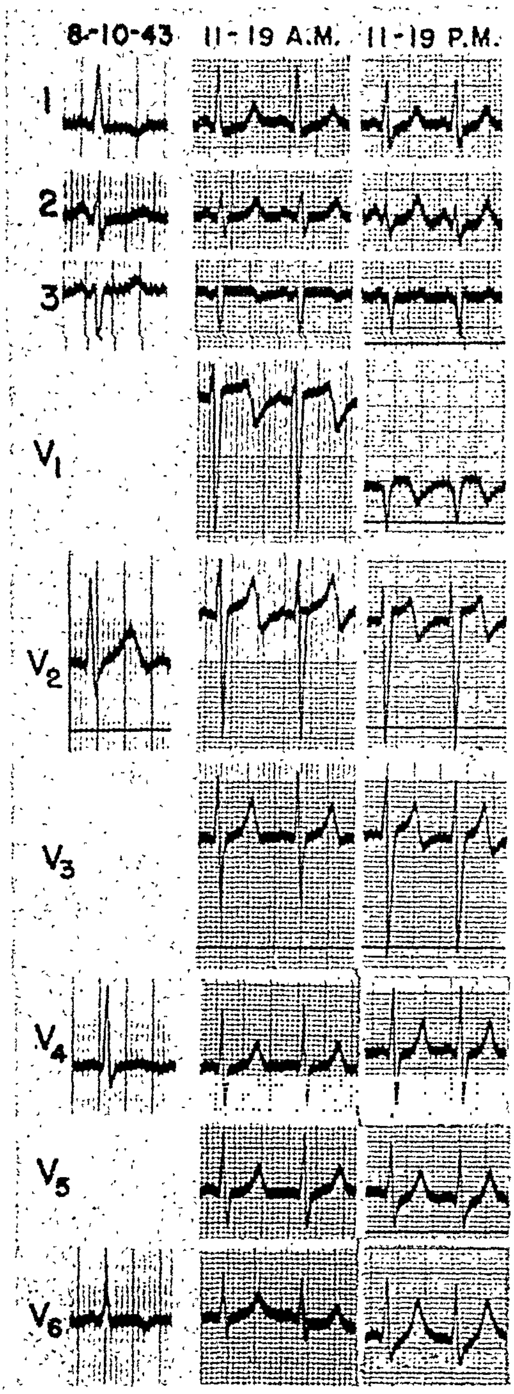

Fig. 1.—Serial electrocardiograms of Case 1 before and after development of high anteroseptal infarction.

deflection in leads over the left ventricle (0.06 second in V_4), the depression of $RS\text{-}T_1$, and the inversion of the T wave in Lead V_6 and Lead I were considered diagnostic of left ventricular hypertrophy. The transitional zone was apparently displaced to the right of Lead V_2. An RS complex was recorded in Lead V_1 on the morning of November 19 and was replaced by a much smaller QS complex in the afternoon. Both tracings were taken in the same posture with similar standardization, and the differences were probably not due to technical errors, since the C_1 position can be accurately located anatomically. For the same reasons, the 50 per cent reduction in the R wave in Lead V_2 was considered significant. In Lead V_1, there was a distinct change from a concave upward RS-T segment and diphasic T wave in the morning tracing to a convex upward RS-T segment and completely inverted T wave in the afternoon. The RS-T junction became more elevated in V_2 and V_3, and the terminal portions of the T waves in these leads became more inverted during the course of the day. The foregoing serial changes in the RST-T complex in Leads V_1, V_2, and V_3 were compatible not only with recent high anteroseptal infarction, but also with acute right ventricular dilatation. Since the QRS changes in Leads V_1, V_2, and V_3 pointed definitely toward the former, an ante-mortem diagnosis was made of a recent infarct localized high in the anteroseptal wall of the left ventricle. The relatively sharp peaking of the T waves raised the question of hyperpotassemia, but this was considered unlikely because the base of the T waves was much broader than is characteristically found. Although the blood potassium was not determined, an elevation sufficient to cause electrocardiographic changes was unlikely, in view of the fact that the blood urea was only moderately elevated to 73 mg. per cent. During the course of the observations on November 19, the RS-T junction in Leads V_4, V_5, and V_6 became depressed. The question arose as to whether this depression was representative of an acute lesion in the subendocardial layer of the anterolateral aspect of the left ventricle or whether it was reciprocal to a coexistent posterior infarction. Although the small initial R_2 disappeared in the afternoon tracing and R_2 became smaller, no elevation of the RS-T segment developed in these leads. Thus, the changes in the standard leads were inconclusive. Unfortunately neither aV_F nor esophageal leads were obtained in this case.

Pathologic Findings.—The heart weighed 480 grams and showed moderate left ventricular hypertrophy. There was no evidence of right ventricular dilatation nor of a pulmonary lesion sufficient to cause acute cor pulmonale. Although not distinctly made out by inspection, a recent patchy infarct was clearly defined microscopically high in the anteroseptal wall of the left ventricle, as demarcated by solid lines in Fig. 2, and a second similar lesion was found at the junction of the lower and middle thirds of the posteroseptal aspect of the left ventricle, as indicated by the broken lines. The patchy anteroseptal infarct was considered responsible for the QRS-T changes in Leads V_1, V_2, and V_3. In the light of our experience with subsequent cases, the developing QS in V_1 and diminishing R in V_2 could be explained best by extension of the anterior infarct into the adjoining septum. The initial R registered in leads over the normal right ventricle is due largely to septal activation[27] and tends to be reduced or eliminated when the septum is infarcted. There was no gross evidence of septal infarction, but the possibility was not excluded, because no microscopic blocks were taken through the septum. Since there was no evidence of a lesion of the apical two-thirds of the anterolateral wall of the left ventricle, the RS-T depression in Leads V_4, V_5, and V_6 was most likely reciprocal to the recent posterior infarction.

CASE 2.—A man, 52 years of age, gave a four-year history of intermittent pain in both wrists, radiating to the shoulders, brought on by exertion and relieved by rest. Since July, 1942, the pain had extended into the chest to reach the sternum. He was first admitted on Nov. 25, 1942, ten hours after the onset of a very severe constrictive retrosternal pain. The hospital course was uneventful, but angina pectoris recurred after resumption of activity. He was awakened by a second severe attack of viselike retrosternal pain on July 26, 1943, and died ten hours later. No cardiac glycosides were given.

Electrocardiographic Findings.—Electrocardiograms selected from a series obtained over an eight-month period are reproduced in Fig. 3. The QS complex consistently present in Lead V_2, together with the classical serial changes in the RS-T segment and T wave of this lead, was diagnostic of anteroseptal infarction. In the first four records of V_4, the deepening T wave, together

with the preservation of a normal initial R, suggested that this lead was reflecting potential variations of an outlying ischemic zone; however, the appearance of a minute Q wave and reduction of the R in later tracings could have been due to the development of a patchy infarction in the subjacent wall or might have been merely due to a slight difference in the position of the electrode with reference to the heart. The tracing of July 26, 1943, was obtained nine hours after the onset of the second attack of pain. From the appearance of a Q_3 together with a markedly elevated RS-T_3, a diagnosis of recent posterior infarction was made. The acute RS-T depression

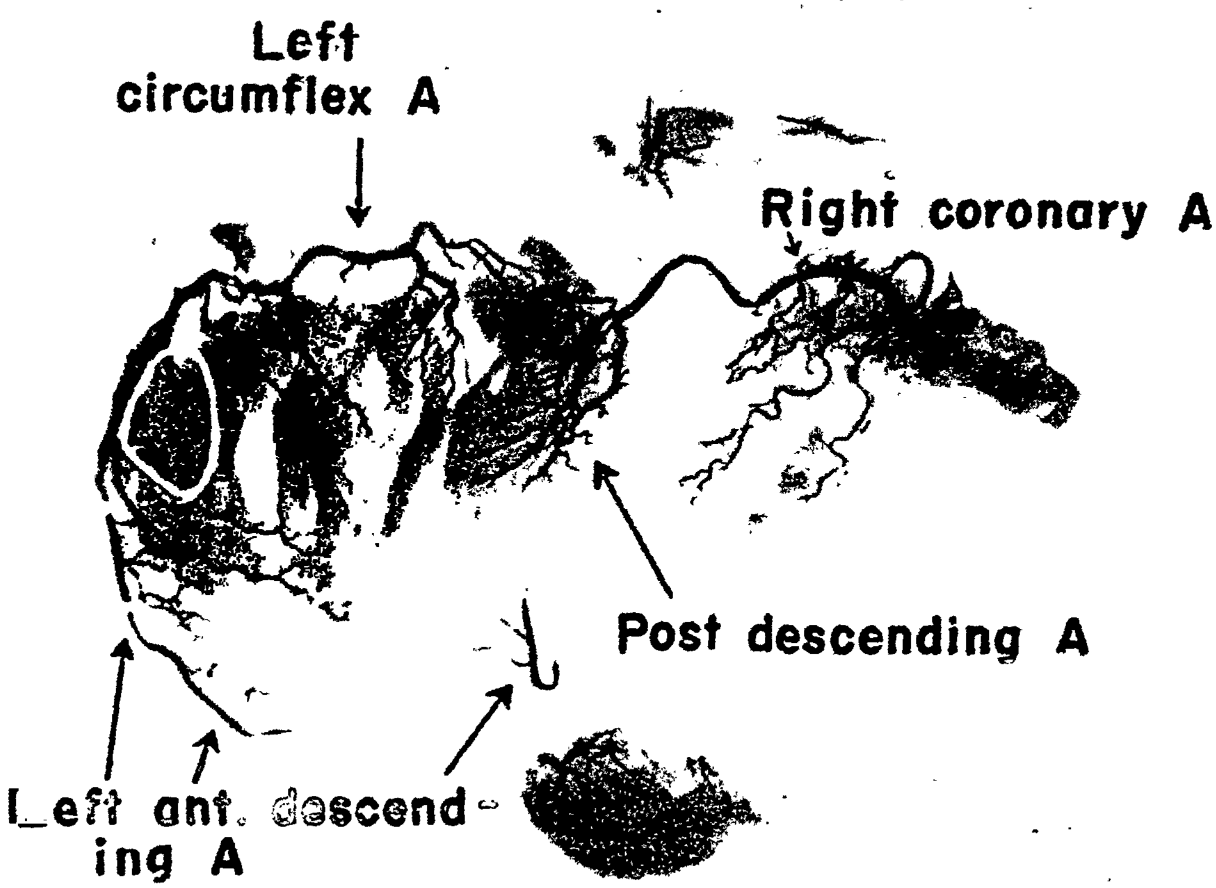

Fig. 2.—Roentgenogram of the heart of Case 1 injected with radiopaque mass and opened by the Schlesinger technique.[27] The recent anteroseptal infarct is demarcated by a solid line and the posteroseptal by a broken line. To assist in orientation in this and all future illustrations in which the Schlesinger technique was used, the arrangement of the heart will be described and anatomical landmarks identified. A longitudinal incision was made through the anterior margin of the right ventricle at its junction with the septum, the latter was removed, and the heart was unrolled and laid flat on the roentgen cassette. The roentgenographic illustrations are arranged with the left ventricle on the reader's left, its anteroseptal margin along with the anterior descending coronary artery forming the left border of the image. When the anterior descending coronary artery continued around the tip onto the posterior aspect of the apex, it was usually severed at the apex by this method of sectioning. The posterior ascending portion of this vessel marked the approximate boundary between the posterior apical aspects of the left and right ventricles, as is evident in Fig. 2. The posterior boundary between right and left ventricles is also indicated by the posterior descending coronary artery and by the sharp difference in density of the ventricular walls. The common origin of the anterior descending and circumflex branches of the left coronary artery is located near the upper left-hand corner of the cardiac image and the origin of the right coronary artery appears near the upper right-hand corner. The course of the left circumflex artery from the anterior to the posterior portion of the groove between the left ventricle and atrium is thus directed from the reader's left toward the center of the cardiac image, whereas the course of the right coronary artery from the anterior to the posterior portion of the groove between the right ventricle and atrium is thus directed from the right toward the center of the roentgenogram. The inferior border of the left ventricular image consists of the anteroseptal portion of the apex on the left, then the lateral, and then the posterior aspects of the apex. The inferior and right borders of the right ventricular image are made up of the severed anteroseptal margin of the right ventricle and the pulmonary artery.

which had developed in Leads V_5 and V_6 was most likely reciprocal to the posterior infarction, but could have been due to extension subendocardially into the lateral wall. Although the T waves had become upright in Leads V_1, V_2, and V_3, the persistence of a QS pattern in these leads was indicative of the old healed infarct of the free anteroseptal wall of the left ventricle and the adjoining interventricular septum.

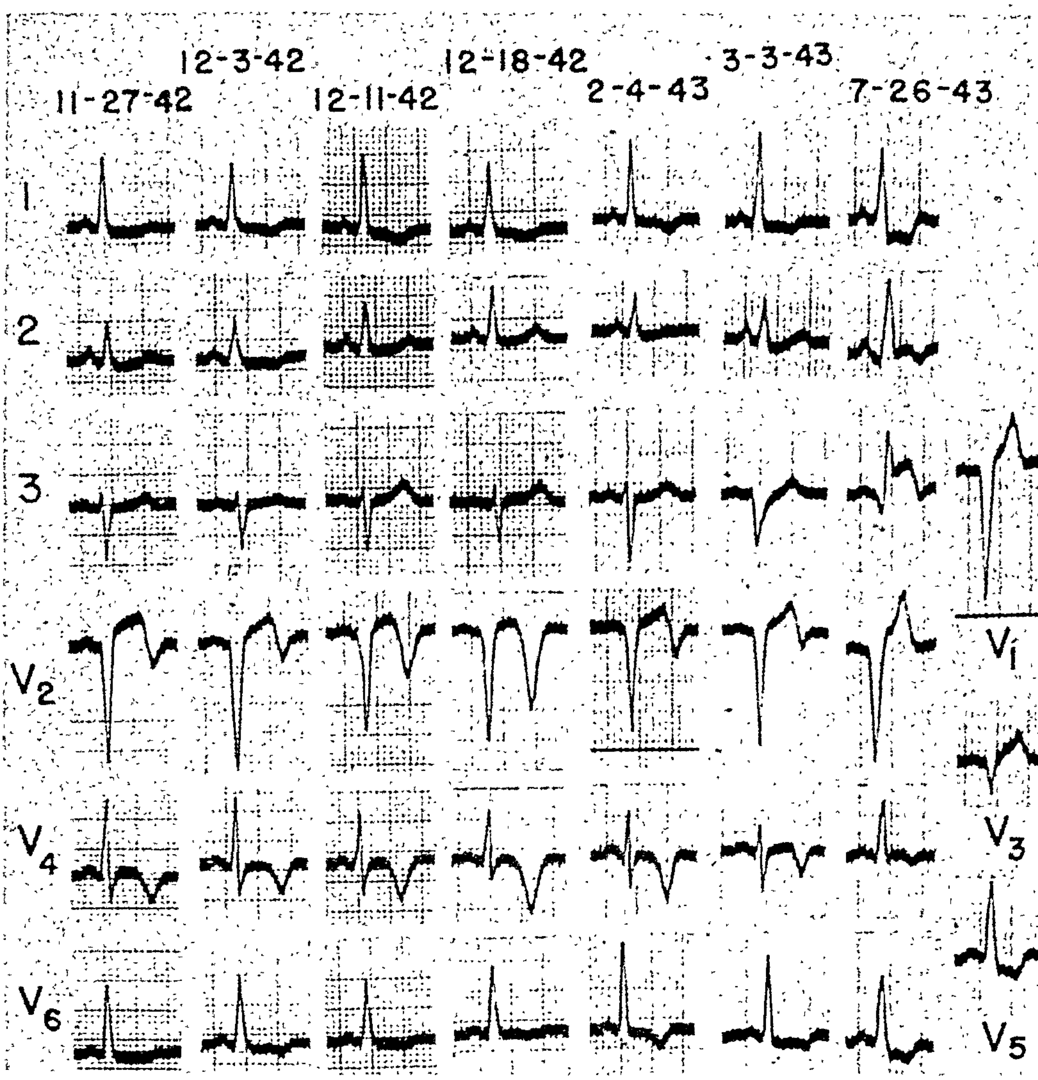

Fig. 3.—Serial electrocardiograms in Case 2.

Pathologic Findings.—The heart weighed 470 grams and exhibited a well-vascularized transmural infarct, involving the apical two-thirds of the anteroseptal wall of the left ventricle, as outlined in Fig. 4, and extending into the contiguous anterior portion of the interventricular septum. The QS complexes in Leads V_1 and V_2 were probably a manifestation of infarction of the anterior portion of the septum. The minute terminal R which followed the deep Q of V_3 was probably derived from preserved subepicardial muscle found in some sections taken through the infarct of the anterior wall. Since the infarct extended to the apex of the anteroseptal aspect of the left ventricle, more definite QRS abnormalities might have been expected in V_4. The ischemic zonal pattern usually recorded in this lead may have been due to counterclockwise rotation sufficient to permit reference of the potential variations of the uninfarcted anterolateral wall to the midclavicular line. The right coronary artery was occluded by a fresh ante-mortem

thrombus at the point marked by an arrow in Fig. 4. Although a number of sections were taken from the posterior walls of the right and left ventricles, no definite evidence of recent posterior infarction could be found. The fact that death occurred ten hours after the onset of pain may account for the lack of histologic change. This case constitutes an example of the electrocardiographic changes preceding the histologic evidence of infarction.[28] There was no histologic evidence of infarction of the lateral wall. The question was left unsettled as to whether the acute RS-T depression in Leads V_5, V_6, and I was reciprocal to the elevation in Lead III or whether it was due to an acute lesion of the subendocardial portion of the lateral wall too early to be recognizable histologically.

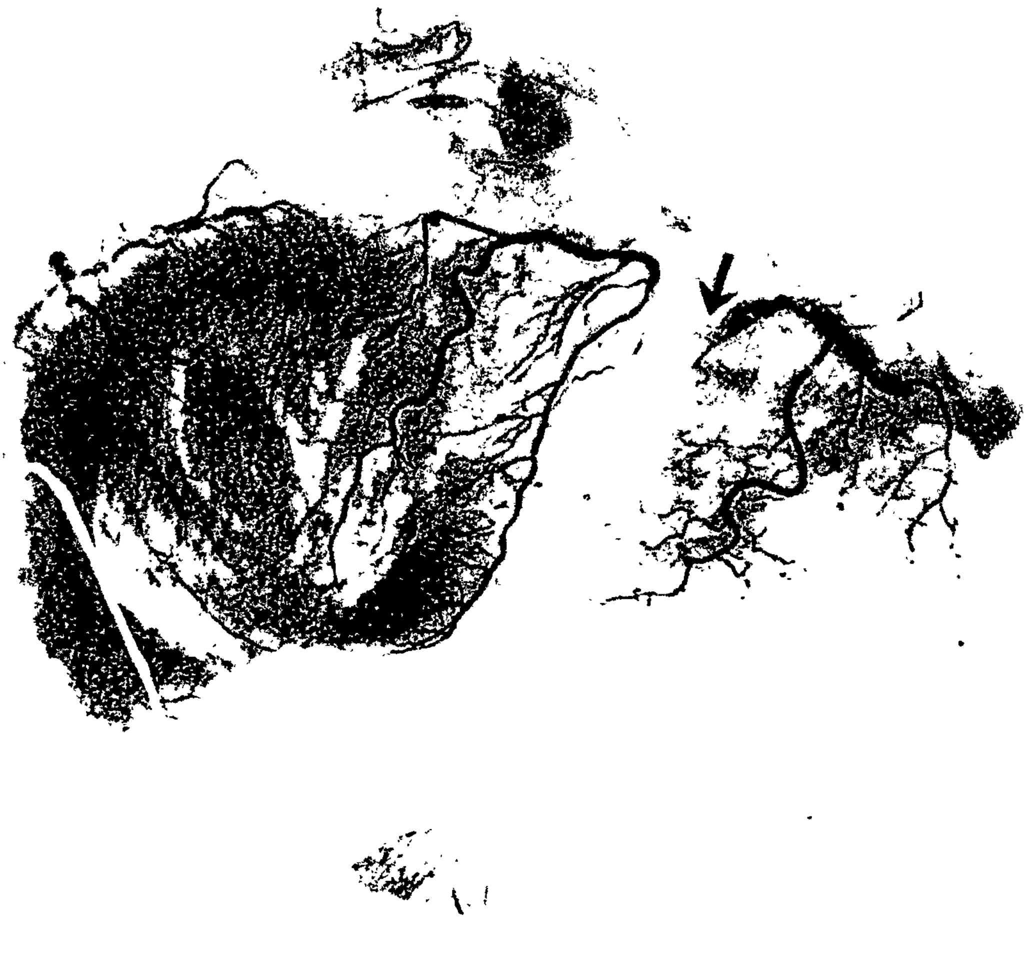

Fig. 4.—Roentgenogram of the injected heart of Case 2.

CASE 3.—A man, 50 years of age, was first hospitalized in August, 1940, because of the recent onset of angina pectoris complicated by congestive failure. He was readmitted in May, 1944, because of recurrent cardiac failure and responded satisfactorily to digitalis. On June 8, 1945, he was suddenly seized with a much more severe and protracted retrosternal oppression accompanied by dyspnea. He was hospitalized for a third time and, on that occasion, there were definite clinical signs of infarction. The daily maintenance dose of 0.1 Gm. of digitalis which he had been taking prior to admission was continued throughout his hospital stay and after discharge. He had no further episodes of protracted retrosternal pain and died on March 25, 1946.

Electrocardiographic Findings.—Electrocardiograms selected from a series taken over a period of one and one-half years are reproduced in Fig. 5. The three standard leads and Lead

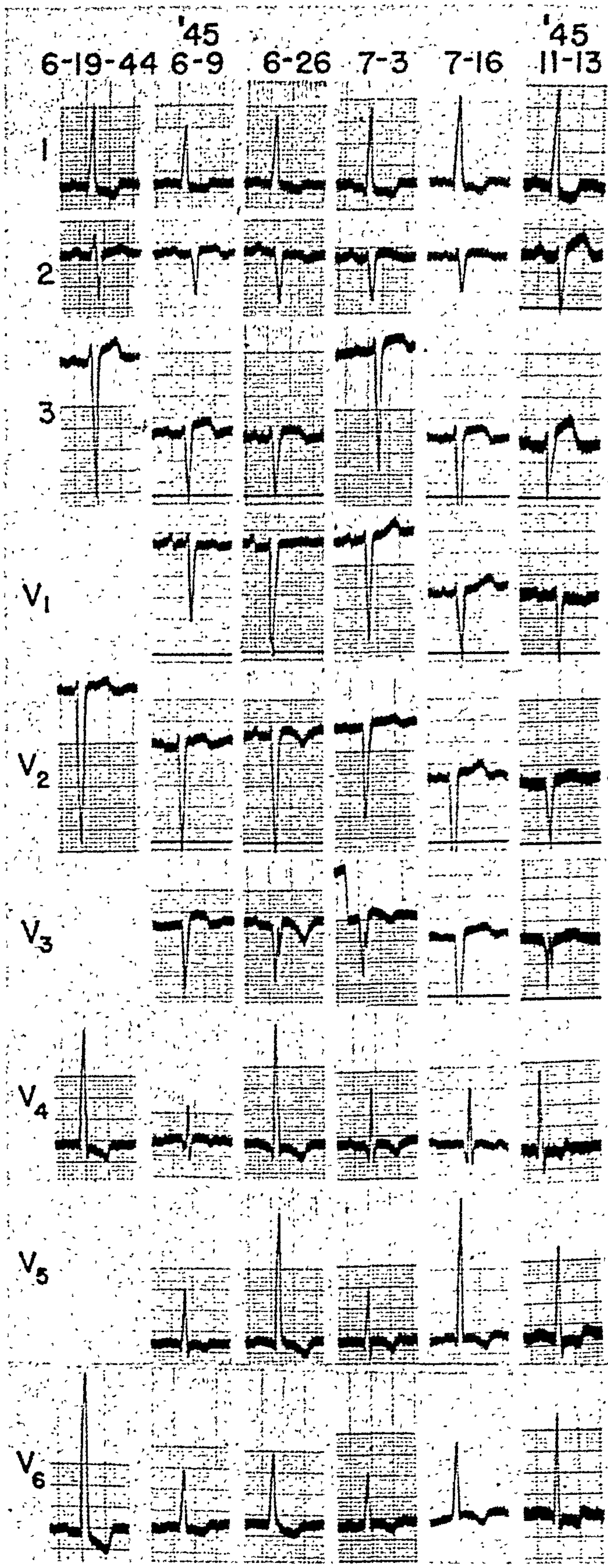

Fig. 5.—Serial electrocardiograms before and after the development of anteroseptal infarction in Case 3.

IVF obtained in August, 1940, were closely comparable to the standard leads and V_4 of June 19, 1944, and consequently were not reproduced. The tall R and slightly delayed intrinsicoid deflection in left ventricular Leads IVF, V_4, and V_6 were attributed to left ventricular hypertrophy; however, a small anteroseptal infarct was not excluded because Lead V_3 was not obtained. The QS complex in V_3 of all tracings taken during 1945 was indicative of anteroseptal infarction, particularly when considered in conjunction with the distinct initial R in V_1 and the smaller R in V_2. The abnormal reduction in the voltage of the R wave in V_2 suggested that this lead reflected the potential variations of a marginal zone of patchy infarction. The serial changes in the RS-T segment and T wave of Lead V_3 during June and July, 1945, were indicative of an organizing infarct. Although the T wave in V_3 later became upright and practically normal in contour, the slurred, notched, or W-shaped QS persisted in this lead as a remnant of the healed anteroseptal infarct. Lead V_4 of the tracings of June 9, July 3, and July 16 displayed a notched or slurred Q wave 0.04 second in duration* and 25 to 33 per cent of the amplitude of the succeeding R. This pattern was attributed to infarction of the subendocardial layer of the anteroapical portion of the left ventricle. The variations on June 26 and November 13 were probably due to a slightly different position of the electrode. The shifting in relationship of electrode to heart on these dates was borne out by the fact that the tracing of June 26 was the only one with an inverted T in V_2 resembling the inverted T of V_3, whereas that of November 13 was the only record with a QS in V_2 comparable to that consistently present in V_3. Leads V_5 and V_6 and the standard leads showed a pattern compatible with left ventricular hypertrophy, but not diagnostic of infarction. Characteristic digitalis effects were present on June 19, 1944, and Nov. 13, 1945.

Pathologic Findings.—The heart weighed 500 grams because of left ventricular hypertrophy. An old healed anteroseptal infarct was found, reaching the apex and extending 6.0 cm. toward the base. The infarct continued into the adjoining septum, but did not involve the lateral wall. The position of the infarct was essentially the same as that in Case 2 (Fig. 4). There was good correlation between the position of the infarct in the anteroseptal portion of the free wall of the left ventricle and the abnormally reduced initial R in V_2, the notched QS in V_3, and the abnormal QR in V_4. The extension of the infarct into the septum had not produced diagnostic changes in Lead V_1. The absence of infarction of the lateral wall was consistent with the premortem ascription of the abnormalities in Leads V_5 and V_6 to left ventricular hypertrophy.

CASE 4.—A man, 58 years of age, a chronic alcoholic, had had hypertension since 1941, intermittent claudication and angina pectoris since 1942, and was first admitted on Oct. 20, 1944, because of severe paroxysms of nocturnal dyspnea and associated retrosternal oppression during the two preceding nights. On the basis of clinical observations in the hospital, recent myocardial infarction was considered unlikely, but could not be definitely excluded. On June 29, 1945, he had an attack of exceptionally severe and protracted retrosternal oppression which led to hospitalization for the next two months. From the clinical course and laboratory findings, a diagnosis of myocardial infarction was made. He was readmitted on Nov. 1, 1945, because of hemiplegia and died three weeks later of bronchopneumonia.

Electrocardiographic Findings.—Electrocardiograms from each of his three admissions are reproduced in Fig. 6. The tracing of Oct. 20, 1944, was obtained thirty-three hours after the first attack of paroxysmal nocturnal dyspnea and before the administration of any cardiac glycosides. This tracing showed a P-R interval of 0.12 second, QRS slurring in the three standard leads, a 0.5 mm. initial R and an exaggerated S wave in Leads V_1 and V_2, and a prominent R wave with slightly delayed intrinsicoid deflection in V_6. The QRS pattern in the precordial leads strongly suggested left ventricular hypertrophy. There was abnormal RS-T depression in Leads V_5 and V_6, but the T waves were upright in all leads and were of relatively high voltage in Leads V_2, V_3, V_4, and V_5. The RS-T depression could have been the result of uncomplicated left ventricular hypertrophy, but was also compatible with a small subendocardial anterolateral infarct. Because of persistent left ventricular failure, digitalis was started on Oct. 22, 1944, and a

*Measurements of the duration of the Q wave represented the time interval elapsing between its onset and nadir, whereas the duration of R represented the time interval from the beginning to the peak of the upstroke.

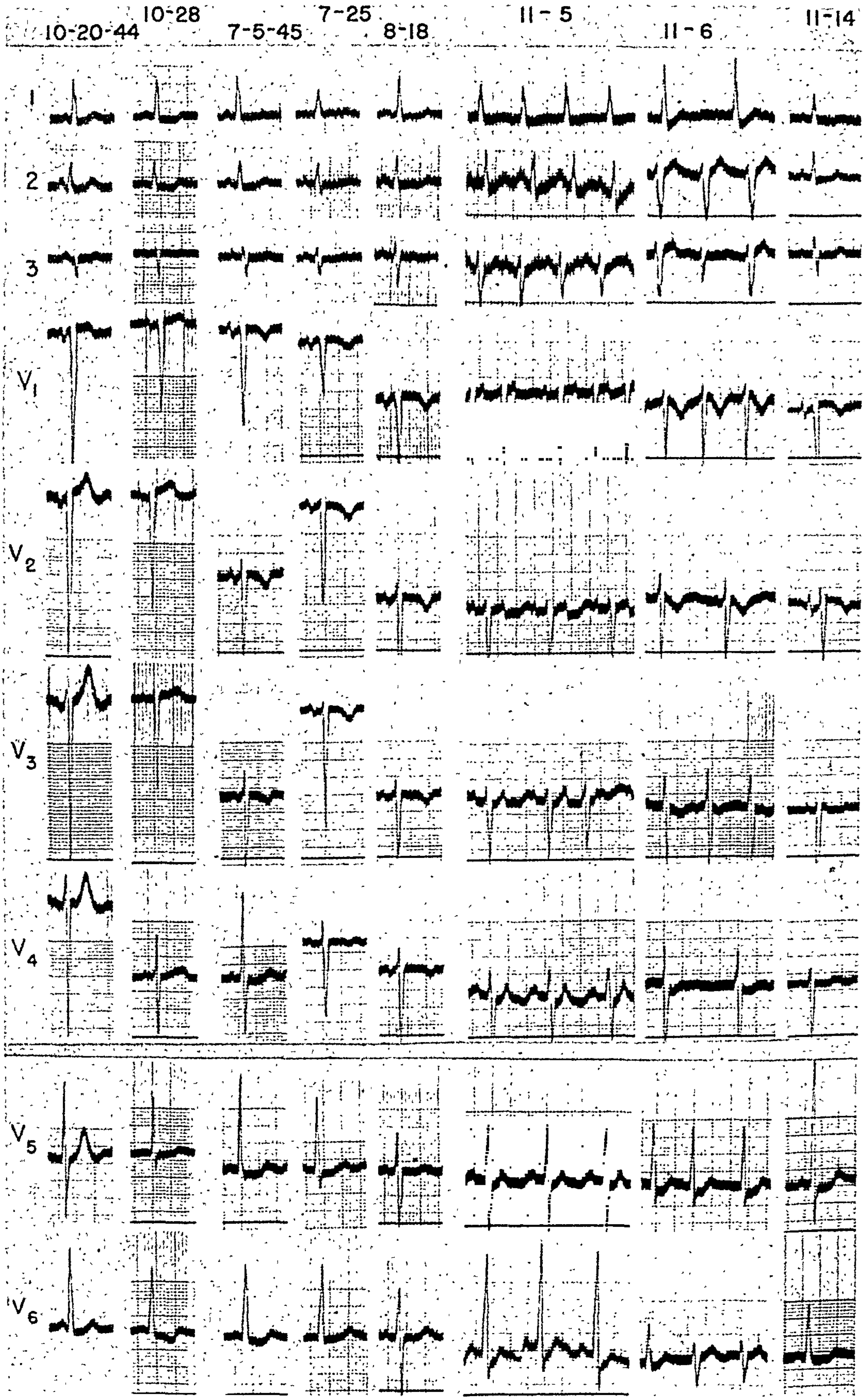

Fig. 6.—Serial electrocardiograms in Case 4.

total of 2.0 Gm. was given prior to the next electrocardiogram on October 28. Since the changes in the RS-T junction and T waves could have been the result of the digitalis, the question as to whether a small infarct had occurred was left unsettled. An unreproduced tracing taken on June 30, 1945, twelve hours after the onset of the pain which led to his second admission, was similar to that of July 5, 1945, except for the presence of upright T waves in Leads V_2 and V_3. The abnormal depression of the RS-T junction in Leads V_4, V_5, and V_6 on June 30 and July 5, 1945, gradually disappeared during the next six weeks. The T waves in Leads V_2 and V_3 became sharply inverted between June 30 and July 5 and remained so throughout the hospital stay. A QS complex was present in Lead V_1, but no abnormal Q waves were found in any precordial or extremity lead. Since no cardiac glycosides were administered during his second hospitalization, a subendocardial anterolateral infarct was considered the most likely cause of the RS-T abnormalities in Leads V_5 and V_6. The T-wave inversion in Leads V_2 and V_3 might have been due to a small intramural anteroseptal infarct, to acute right ventricular dilatation, or to localized pericarditis, but the first alternative was favored because of the late development and persistence of the findings. It is noteworthy that serial records of the standard leads gave no evidence of either infarct. The tracing of November 5, which was taken before the administration of cardiac glycosides, revealed an auricular tachycardia with variable block. On November 6, following the administration of 1.6 Gm. of Cedilanid, a transient auricular fibrillation with ventricular extrasystoles developed and sinus rhythm was then restored. From the contour of the RS-T segments and shortening of the Q-T interval, it is probable that the RST-T changes were due to Cedilanid. Attention is drawn, however, to the fact that the R wave in V_3 of November 14 was smaller than that of V_2. This might have been a remnant of the earlier anteroseptal infarction.

Pathologic Findings.—The heart weighed 577 grams and showed rather marked left ventricular hypertrophy. Gross inspection revealed two separate areas of scarring, as demarcated in Fig. 7. One of these lay intramurally in the anteroseptal aspect of the second and third segments from the apex; the other occupied the subendocardial one-third of the anterolateral aspects of the third and fourth segments. By microscopic examination, these were regarded as healed infarcts of several months' duration. From the electrocardiograms, it is probable that the anteroseptal infarct occurred in July, 1945. The fact that the infarct was limited to the mid-portion of the wall is in keeping with the absence of Q waves and the isolated T-wave abnormalities. The subendocardial anterolateral infarct could have occurred on either the first or second admission, but more likely at the latter time because of the more typical changes in the RS-T segment. The absence of abnormal Q waves in Leads V_5 and V_6 may have been due to the relatively small size of the infarct in comparison with the bulk of the surrounding uninfarcted muscle.

CASE 5.—A hypertensive man, 72 years of age, was admitted in coma following a cerebral hemorrhage. His blood pressure on the day of admission ranged from 240/110 to 300/150. During the second night of hospitalization, peripheral circulatory collapse developed and the blood pressure fell to 140/70. The patient did not regain consciousness and died forty-seven hours after admission from the cerebral vascular accident.

Electrocardiographic Findings.—An electrocardiogram taken after the administration of 0.8 mg. Cedilanid and eight hours before death is reproduced in Fig. 8,*A*. Close scrutiny of Lead V_1 revealed a Q wave 0.5 mm. deep followed by a 1.5 mm. R wave and a notched S wave 10 mm. deep. Although a QS deflection may occur as a normal variant in V_1, a Q preceding an RS complex is abnormal and is representative of septal infarction. Lead V_2 exhibited a QS complex with a coarse notch near the base of the descending limb. This finding, taken in conjunction with the pattern in V_1, was attributed to infarction of the septum and adjoining anteroseptal wall at the base of the left ventricle. The RS-T junction was depressed in V_1 and V_2 and the segment sloped straight downward in a manner suggestive of digitalis effect. In view of the fact that the Q-T interval was at the upper limits of normal (0.32 second at a rate of 110 per minute), it was believed that the administered Cedilanid was not the major cause of the changes in the RS-T segment and T wave. The depression of the RS-T junction and contour of the segment were strongly suggestive of the changes produced by acute infarction confined to the subendocardial layer. In Lead V_3 there was a 2.5 mm. Q wave, followed by R and S waves, each of 15 mm., and by a

sharply inverted T wave. Since the Q decreased and then disappeared in leads farther to the left, the Q in V_3 was regarded as abnormal and referable to a thin marginal zone of subendocardial infarction. The tall R and sharply inverted T waves of Leads V_4 and V_5 were attributed to an outlying zone of ischemia rather than to left ventricular hypertrophy because of the normal QRS-T pattern in V_6. The standard leads showed marked left axis deviation, but were not diagnostic of infarction.

Fig. 7.—Roentgenogram of the heart of Case 4 injected with radiopaque mass and cut into transverse slices approximately 1 cm. thick. The position of the intramural anteroseptal infarct is indicated by the solid line and the location of the anterolateral infarct, by the broken line. In this and in all other illustrations of transversely sectioned hearts, the apical segment is located in the upper left-hand corner and the intervening segments are arranged in rows from left to right and then from above downward, ending with the basal segment, which includes the valular ring, in the lowermost row. Each slice is arranged so that the anterior surface of the ventricles is uppermost and the lateral wall of the left ventricle is on the reader's left. In the descriptions the apex is referred to as the first segment and the remainder are numbered consecutively toward the base.

Pathologic Findings.—The heart weighed 516 grams as a result of left ventricular hypertrophy. A relatively small infarct was found in the fourth and fifth segments, involving the subendocardial two-thirds of the anteroseptal wall of the left ventricle and the adjoining left side of the septum, as outlined in Fig. 9. There was microscopic evidence that the infarct had been present for two weeks or more. Thus, the QRS pattern in Leads V_1, V_2, and V_3 was well correlated with the location of the infarct at autopsy and the thickness of the wall involved; however, the impression that the infarct was very recent in origin and probably secondary to the precip'tous fall in blood pressure was incorrect. In the final analysis, there was uncertainty as to whether the RS-T pattern in Leads V_1 and V_2 was chiefly a residue of subendocardial injury or chiefly a result of Cedilanid.

Case 6.—A man, 56 years of age, collapsed on the street and was admitted to the hospita in coma with a blood pressure of 240/140 and a rapid, totally irregular ventricular rhythm. Be

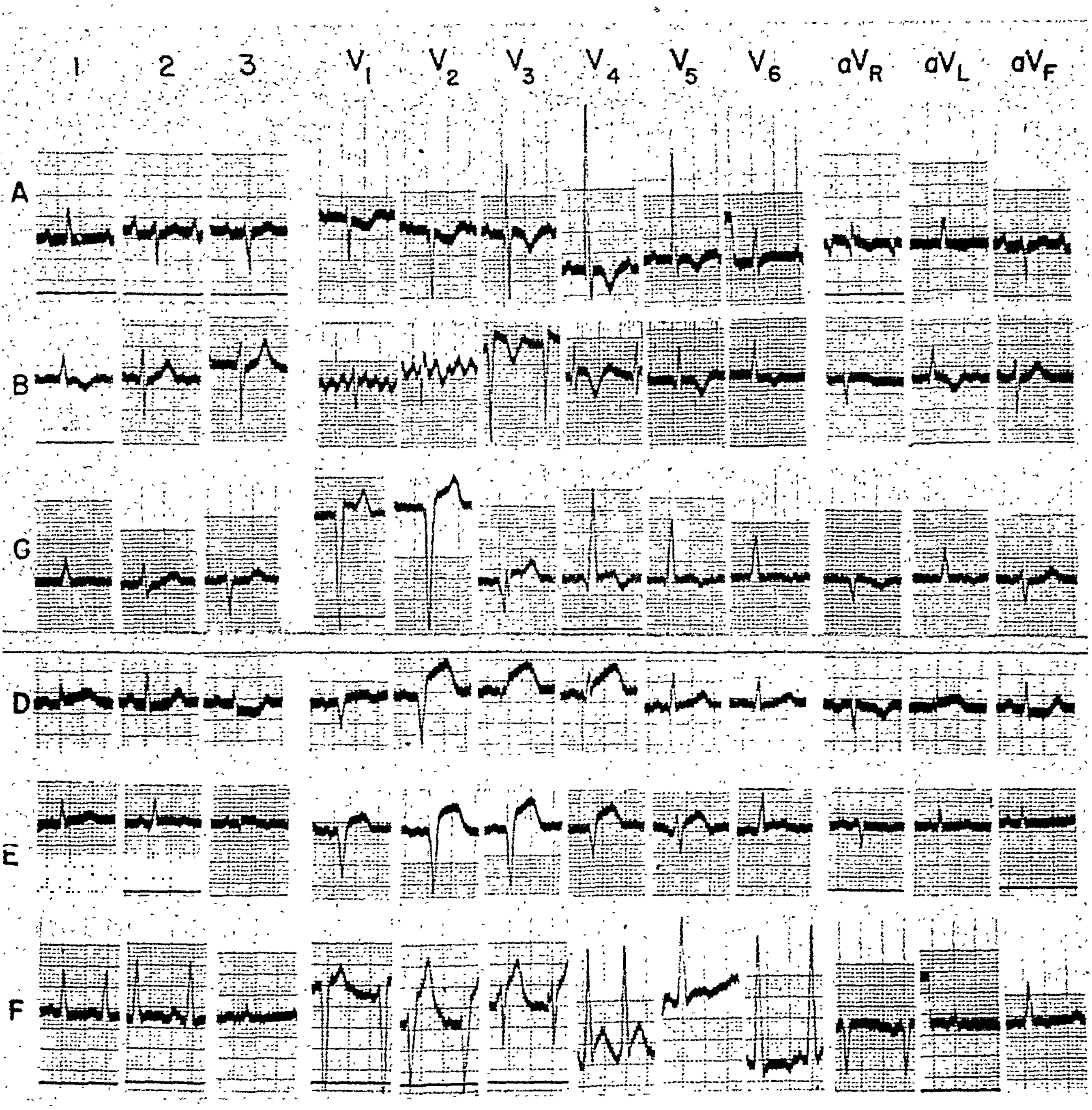

Fig. 8.—Recent anteroseptal infarction. *A*, Case 5; *B*, Case 6; *C*, Case 7; *D*, Case 8; *E*, Case 9; *F*, Case 10.

cause of repeated Jacksonian convulsions, a 500 c.c. phlebotomy was done, following which the blood pressure fell progressively to 85/70. No cardiac glycosides were given. The patient did not regain consciousness and died from the cerebral vascular accident forty hours after admission.

Electrocardiographic Findings.—An electrocardiogram obtained shortly after the blood pressure had fallen to shock levels and twenty-one hours before death is reproduced in Fig. 8,*B*. Although high voltage F waves due to an auricular circus movement overlay the QRS-T complex in Leads V_1 and V_2, a close study of the latter revealed a definite initial R wave in Lead V_1, measuring about 3.0 mm. in amplitude, and a deep Q and a late R in V_2. The T wave in Lead V_1 was completely obscured, but that in V_2 was clearly inverted. Lead V_3 exhibited a QS complex of central zonal type, an abnormally elevated RS-T junction, and cove-shaped inversion of the T wave. Lead V_4 showed a Q wave of 1.0 mm., an R wave of 7.0 mm., and an S wave of 3.0 mm. with elevated RS-T junction and cove-shaped inversion of the T wave representative of a marginal

zone. From the QRS changes, a diagnosis was made of a small transmural anteroseptal infarc situated nearer the apex than in Case 5, and from the RST-T pattern the infarct was considere recent in origin and accompanied by injury to the subepicardial layer. The standard lead showed left axis deviation with inversion of T_1, but were not diagnostic of infarction.

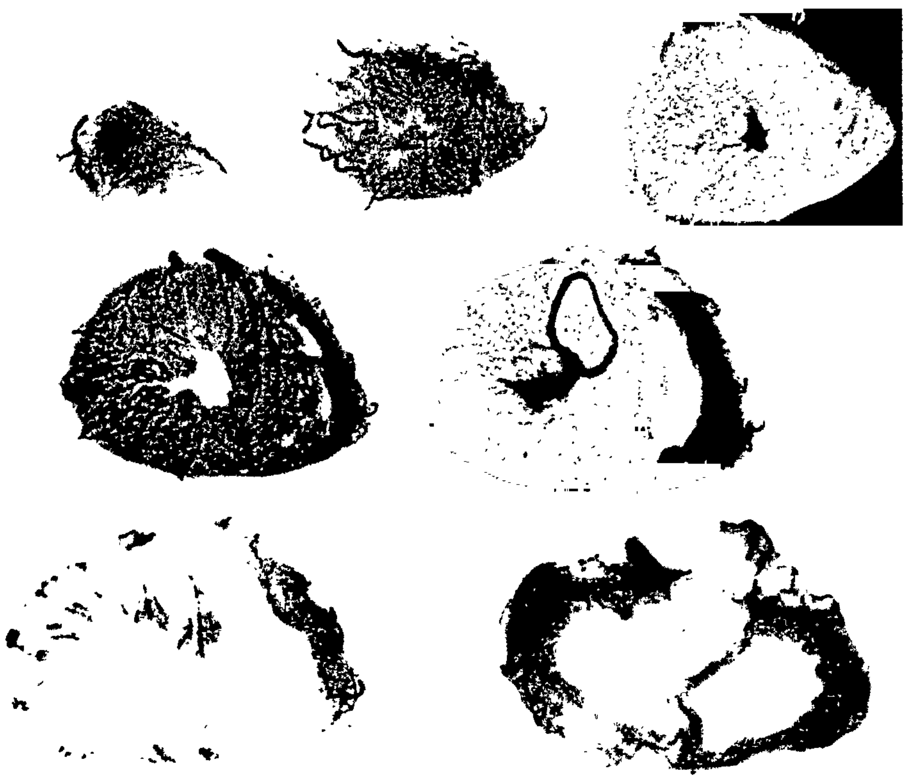

Fig. 9.—Roentgenogram of the heart of Case 5, showing high anteroseptal infarct outlined in black.

Pathologic Findings.—The heart weighed 501 grams because of left ventricular hypertrophy. An infarct was not seen grossly, but by means of multiple microscopic blocks was found to be present in the areas outlined in Fig. 10. The infarct was transmural in the fourth segment and involved the subendocardial one-half to three-fourths of the second and third segments. The age of the lesion was judged to be approximately twenty-four hours. Thus, the electrocardiographic and the autopsy findings were in close agreement both as to the location and the age of the infarct.

CASE 7.—A man, 58 years of age, gave a history of abrupt congestive failure nine months previously. He had had no thoracic pain until two days before admission when he was seized with severe constriction just to the right of the sternum. During the interim he was unable to pass urine, which was his chief complaint on admission. Physical examination revealed congestive failure complicated by circulatory collapse. Death occurred on the second hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained on the first hospital day, after the administration of 1.2 mg. Cedilanid, is reproduced in Fig. 8,*C*. In Lead V_1 there was a distinct initial R wave 1.0 mm. in height, followed by a deep, broad S wave compatible with left ventricular hypertrophy. The deep QS complex in Lead V_2 and the deep, broad Q and late R in V_3 were diagnostic of anteroseptal infarction. Although the Q wave in Lead V_4 was only ten per cent of the amplitude of the succeeding R, the time interval of 0.04 second from its onset to its nadir indicated that it was abnormal and attributable to a marginal zone of subendocardial infarction. In Leads V_2 and V_3 the RS-T junction was abnormally elevated, but the contour

of the RS-T segment and T wave was not typical of recent infarction. On the other hand, the inverted T waves of Leads V_4 and V_5 were suggestive of recent infarction and were probably independent of Cedilanid because of the abnormally prolonged Q-T interval. The standard leads were not diagnostic of the anteroseptal infarct, which was clearly revealed by the precordial leads.

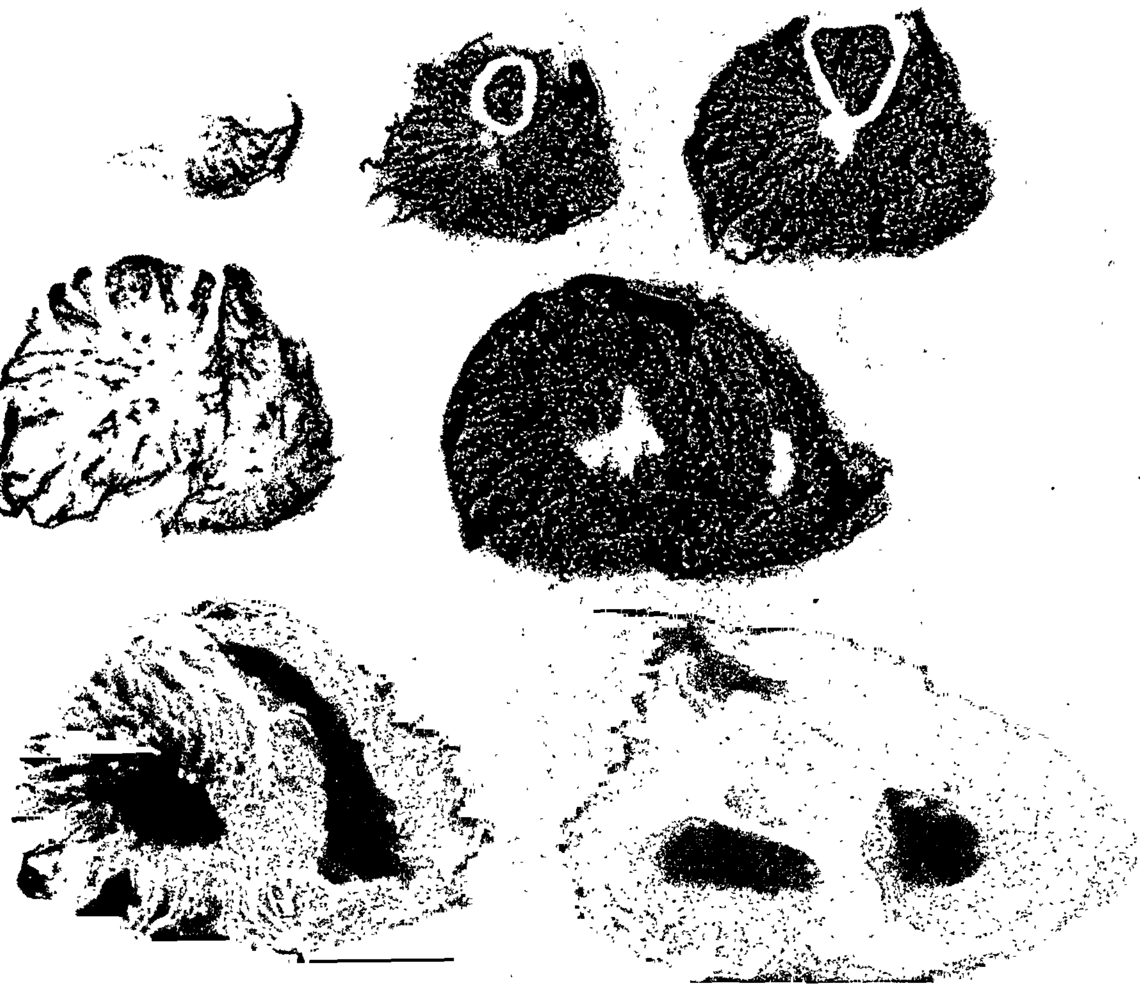

Fig. 10.—Roentgenogram of the heart of Case 6 with infarct outlined in black.

Pathologic Findings.—The heart weighed 543 grams because of left ventricular hypertrophy. A fusiform infarct was found in the apical 6.0 cm. of the anteroseptal wall of the left ventricle comparable in size and position to that of Case 2 (Fig. 4). The lateral wall was uninvolved. On microscopic examination, an old healed infarct involved the subendocardial one-third and a recent extension was found chiefly in the mid-zone of the myocardium, but projected in fingerlike fashion to the epicardium. The position of the infarct at autopsy and the thickness of the wall involved were thus in general agreement with the electrocardiographic predictions. The unusually tall R in Lead V_4 did not correspond with the fact that the infarct reached the anterior aspect of the apex. In view of the counterclockwise rotation, it may have been derived, in part, from the potential variations of the epicardial surface of the uninfarcted lateral wall.

CASE 8.—An obese diabetic woman, 43 years of age, was awakened at 4:00 A. M. by a severe retrosternal pain which radiated down both arms and was accompanied by repeated vomiting. The patient was hospitalized four hours later, but the pain continued despite frequent doses of morphine. No cardiac glycosides were given. Death occurred twelve hours after the onset of the present illness.

Electrocardiographic Findings.—An electrocardiogram obtained seven hours after the onset of the pain is reproduced in Fig. 8,*D*. A QS complex, which was slurred on its descending limb, was present in Leads V_1 and V_2; a splintered QRS of low voltage, which commenced with a Q wave, was found in V_3; and a Q wave of 1.5 mm., followed by a slurred R of 5.0 mm., was present in Lead V_4. The RS-T junction was markedly elevated in Leads V_2, V_3, and V_4, and the contour of the RS-T segment and T wave in these leads was typical of the stage of injury. The RS-T junction was very slightly elevated in Lead V_5, but the ventricular complex in Leads V_5 and V_6 was considered to be within normal limits. A diagnosis of very recent transmural anteroseptal infarct was thus made from the precordial leads. The standard leads in this case were indicative of anterior infarction, despite the fact that no signs were found in Leads V_5 and V_6. The reason for this was apparent from the unipolar limb leads. The pattern in aV_L corresponded closely to that in V_3, indicating that the potential variations of the infarcted anteroseptal wall of the left ventricle were referred to the left arm, rather than those of the uninfarcted lateral wall, as in the preceding cases. The pattern in aV_L was carried over into Lead I, accounting for the abnormal RS-T elevation. Judging from the QRS in aV_F, the potential variations of the posterior diaphragmatic surface of the left ventricle were referred to the left leg. The reciprocal RS-T depression in this lead was typical of that recorded over the intact wall opposite an acute infarct and was carried over into Lead III.

Fig. 11.—Roentgenogram of the heart of Case 8, showing rupture of the anterior wall in the second segment

Pathologic Findings.—The heart weighed 400 grams and exhibited a very recent transmural infarct involving the apical two-thirds of the anterior wall of the left ventricle and extending into the anterior two-thirds of the septum, as outlined in Fig. 11. Death was due to rupture of the anterior wall above the apex, as evident in the second segment of the roentgenogram. Since

Positions C_1 and C_2 were presumably over the uninfarcted right ventricle, the absence of the initial R from Leads V_1 and V_2 was correlated with the infarction of the septum and ascribed to obliteration of the positive potentials ordinarily referred to the right side of the precordium during septal activation. The RS-T displacement in Leads V_1 and V_2 was attributed to injury to the septum. The abnormal Q wave in Leads V_3 and V_4 was the result of the infarction of the anteroseptal wall of the left ventricle. In view of this apparently complete transmural necrosis, the presence of a rudimentary R in V_3 and a definite R in V_4 is noteworthy. The latter was most likely derived from the uninfarcted lateral wall. The involvement of the apex at autopsy was more extensive than had been anticipated from the presence of the distinct R in Lead V_4 and the practically normal QRS-T pattern in Lead V_5.

CASE 9.—A man 58 years of age, a chronic alcoholic, was admitted in an intoxicated state, complaining of acute retrosternal constriction and dyspnea. He gave a history of a similar attack two months previously which had lasted only one-half hour. No cardiac glycosides were given. Hospital course was uneventful until the sixth day when he suddenly died.

Electrocardiographic Findings.—An electrocardiogram obtained approximately forty-eight hours after the onset of the present illness is reproduced in Fig. 8,*E*. Leads V_1, V_2, and V_3 exhibited a QS, an abnormally elevated RS-T junction, and a monophasic upright T wave indicative of a recent transmural infarct involving the anteroseptal wall of the left ventricle and the adjacent septum. A definite but small initial R wave was present in Leads V_4 and V_5 along with an abnormally high RS-T take-off, suggesting a marginal zone of patchy infarction reaching the epicardium. The RS-T junction in the complex of Lead I reproduced in the illustration showed a pseudo elevation due to upward drifting of the string, but in other cycles of this lead the RS-T was isoelectric and the ventricular complex within normal limits. The small QR_3, slightly elevated RS-T_3, and inverted T_3 raised the question of posterior infarction; however, a study of the Goldberger leads showed a normal QRS pattern in Lead aV_F and indicated that Q_3 was derived from the initially positive potentials of the left arm and thus not due to posterior infarction.

Pathologic Findings.—The heart weighed 447 grams because of left ventricular hypertrophy. A recent transmural infarct involving the apical two-thirds of the anteroseptal aspect of the left ventricle and adjacent interventricular septum was found; the infarct was comparable in size and location to that in Case 8 (Fig. 11). The lateral and posterior walls of the left ventricle were not involved. Electrocardiographic and pathologic findings were in agreement both as to the location and age of the infarct.

CASE 10.—A man, 74 years of age, was admitted with extreme orthopnea and cyanosis. History was unobtainable. Examination revealed left ventricular hypertrophy, Type 3 pneumonia, and peripheral circulatory collapse. No cardiac glycosides were given prior to the taking of the electrocardiogram. The patient died of the pneumonia seven hours after admission.

Electrocardiographic Findings.—An electrocardiogram obtained shortly after admission is reproduced in Fig. 8,*F*. The initial deflection of the QRS was upright in all precordial leads. The amplitude and duration of the R wave in Lead V_6 were indicative of left ventricular hypertrophy. The striking feature was an abnormal RS-T elevation, which amounted to 7.0 mm. in Lead V_2, 4.5 mm. in V_3, and 3.0 mm. in V_4. The RS-T displacement in Leads V_2 and V_3 was much greater than that encountered in leads from the right precordium in the presence of uncomplicated left ventricular hypertrophy. Two possibilities were strongly considered: a pericarditis secondary to pneumonia and a recent anteroseptal infarct. The contour of the RS-T segment was typical of pericarditis, but the degree of elevation in Lead V_2 was greater than is generally produced by such a lesion. Furthermore, the limitation of the RS-T displacement to the first four precordial leads was against an inflammatory lesion, which because of its diffuse distribution would be expected to produce RS-T elevation in Leads V_5 and V_6 and in Lead aV_F as well. Thus, a diagnosis of recent anteroseptal infarct was favored, despite the atypical contour of the RS-T segment and the initial upright phase of the QRS. The absence of a Q wave was compatible with an infarct limited to the subepicardial layer or with an infarct distributed in patchy fashion through the wall. The standard leads showed low voltage of the T waves, but were not diagnostic of infarction.

Pathologic Findings.—The heart weighed 506 grams because of left ventricular hypertrophy There was no evidence of pericarditis. An infarct was found by gross examination in an area corresponding to that of Case 2 (Fig. 4). Microscopic examination revealed that the infarct was patchy in distribution and was in part, old and in part, recent. The recent extension in the area of old infarction was probably a complication of the circulatory collapse consequent upon the pneumonia. The absence of Q waves may have been the result of the patchy character of the infarct. There was satisfactory correlation between the RS-T displacement in the electrocardiogram and the location of the recent infarct at autopsy.

CASE 11.—A man, 54 years of age, gave a history of anorexia and repeated vomiting of approximately two weeks' duration, right-sided pleural pain, scantily productive cough, and fever of two days' duration. There were physical and laboratory signs of right middle lobar pneumonia and uremia, the blood urea being 334 mg. per cent. At 2:00 A. M. following admission, he was awakened by extreme dyspnea without associated pain. Physical examination showed marked bilateral pulmonary edema. No cardiac glycosides were given. The patient died in circulatory collapse forty-four hours later.

Electrocardiographic Findings.—An electrocardiogram obtained eight hours after the attack is reproduced in Fig. 12,*A*. In Leads V_{3R} and V_1 there was a deep Q followed by an upstroke which extended 4.0 to 5.0 mm. above the isoelectric line. The RS-T segment sloped gradually downward to end in a sharply inverted T wave. Reciprocal, sharply peaked, upright T waves were present in Leads V_3, V_4, and aV_F, whence they were carried over into Leads II and III. The problem arose during life as to whether these electrocardiographic findings were the result of a recent high anteroseptal infarction, acute cor pulmonale secondary to the pneumonia, or hyperpotassemia associated with uremia. The deep Q, late R, and markedly elevated RS-T junction in Leads V_{3R} and V_1 pointed strongly toward high anteroseptal infarction and were not adequately explained by either of the other alternatives. Furthermore, the base of the T wave was too wide and the apex not sufficiently pointed to be characteristic of hyperpotassemia. The standard leads showed a prominent S pattern and were not diagnostic of infarction.

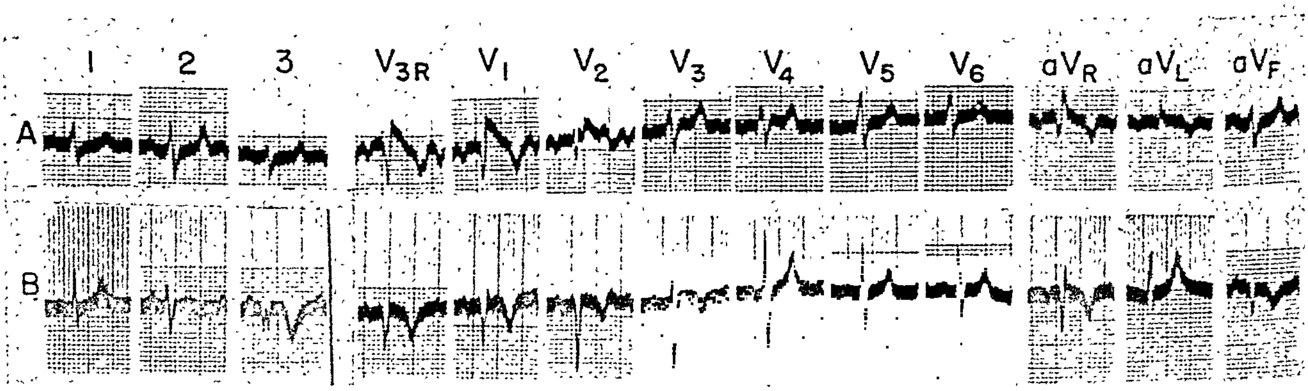

Fig. 12.—Recent anteroseptal infarction. *A*, Case 11; *B*, Case 12.

Pathologic Findings.—Both lungs were markedly edematous and a right middle lobar consolidation was present. There was no evidence of pulmonary embolism. The heart weighed 420 grams and exhibited slight left ventricular hypertrophy. The right ventricle was not hypertrophied nor appreciably dilated. An infarct was not seen grossly, but was found microscopically in the two basilar segments occupying the anteroseptal wall of the left ventricle, the anterior portion of the septum, and the adjacent margin of the right ventricle, as outlined in Fig. 13. The infarct was estimated to be of two days' duration. The poor injection of the anterolateral wall of the left ventricle was due to a technical error, since the left coronary artery was not occluded and multiple microscopic sections outside of the area outlined were negative. The recent infarction of the anterior part of the base of the septum and the immediately adjoining walls of the

right and left ventricles could adequately account for the absence of the initial R and the localized RS-T elevation in Leads V_{3R} and V_1.

CASE 12.—A man, 40 years of age, was well until Sept. 11, 1946, when he was suddenly seized with stabbing pain in the left axilla, aggravated by breathing and accompanied by dyspnea. He recovered completely and was well until October 5, when he was suddenly taken with a similar pain in the right axilla, leading to admission the next day. X-ray films of the lungs revealed a small area of consolidation in the right base. The heart was negative and the blood pressure 122/80. Hospital course was uneventful until 4:30 A. M. on October 12, when he was awakened by constrictive retrosternal pain and failed to rally, expiring thirteen hours later. No cardiac glycosides were given.

Fig. 13.—Roentgenogram of the heart of Case 11, showing recent high anteroseptal infarct outlined in black.

Electrocardiographic Findings.—An electrocardiogram obtained nine hours before death is reproduced in Fig. 12,*B*. Lead V_{3R} showed a QS deflection, a very slightly elevated RS-T junction, and a sharply inverted T wave; Lead V_1 displayed a deep Q, minute terminal R, and similar RST-T complex; Lead V_2 exhibited a minute initial R and a less deeply inverted T wave. In Lead aV_F a comparable T wave was found together with a QS complex, which exhibited a slight notch near the base of the descending limb. The question arose as to whether the pattern in Leads V_{3R}, V_1, V_2, and V_3 was due to pulmonary embolism or to anteroseptal infarction. The absence of a distinct initial R in Leads V_{3R} and V_1 pointed toward the latter, but a positive differentiation could not be made from a single electrocardiogram. It was most unfortunate that a tracing had not been obtained prior to the terminal episode. The pattern in Lead aV_F may have

been due to transmission of potential variations of the epicardial surface of the anteroseptal area to the left leg or may have been representative of extension of the infarct through the septum to the posterobasal portion of the left ventricle. The findings in Leads I and III were similar to those in Leads aV_L and aV_F, respectively, and gave no additional help in diagnosis.

Pathologic Findings.—A healed pulmonary infarct 1.5 cm. in diameter was found at the periphery of the left upper lobe. A slightly larger organizing infarct of about one week's duration was found near the periphery of the right middle lobe. No evidence of other pulmonary infarcts or terminal pulmonary embolism was uncovered. The heart weighed 350 grams and showed moderate right ventricular dilatation, but no hypertrophy. By means of multiple microscopic blocks, a very early patchy infarct was found distributed through the entire thickness of the basal three-fifths of the septum and extending through the adjoining anterior and posterior walls in the fourth and fifth segments, as outlined in Fig. 14. The infarct did not involve the outer

Fig. 14.—Roentgenogram of the heart of Case 12, showing position of infarct in black outline.

wall of the right ventricle. Hence, both the pulmonary embolism and acute anteroseptal infarction that had been considered during life were found at autopsy. Judging both from the reports of others and our own experience, the portion of the pulmonary arterial bed obliterated by emboli was too small to account for the striking changes in the QRS-T complex of Leads V_{3R}, V_1, and V_2. Thus, the findings in these leads were probably produced by the acute infarct of the interventricular septum and adjoining anteroseptal wall of the left ventricle. The findings in Lead aV_F were most likely the result of extension of the infarct into the posterobasal portion of the left ventricle.

Case 13.—A woman, 95 years of age, died of pneumonia complicating a fractured femur. No history of myocardial infarction was obtained and no cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram taken three days before death is reproduced in Fig. 15,*A*. A QS complex was recorded in Leads V_1 and V_2. Since such a pattern may occur as a normal variant in V_1 and V_2 in conjunction with an upright initial deflection in leads farther to the left, the interpretation of the QS of V_1 and V_2 in this case depended upon the findings in the remaining leads. A Q wave approximately 0.03 second in duration and 25

Fig. 15.—Old healed anteroseptal infarct. *A*, Case 13; *B*, Case 14; *C*, Case 15; *D*, Case 16; *E*, Case 17; *F*, Case 18.

per cent of the amplitude of the succeeding R wave was present in Leads V_3 and V_4. It is noteworthy that the Q wave in Leads V_3 and V_4 not only had a greater absolute duration and amplitude than that in V_5 and V_6, but also was larger in proportion to the R wave of the same leads. Since the Q waves in Leads V_3 and V_4 were thereby established as abnormal, the QS complexes in V_1 and V_2 were attributed to anteroseptal infarction. In view of the normal contour

of the RS-T segment and T wave, the infarct was considered to be old. The Q wave of 1.0 mm. and the R wave of 3.5 mm. in Lead I raised the question of old lateral infarct. Examination of the unipolar extremity leads showed that the heart was in vertical position. The inverted P wave in Lead aV_L suggested that the QS pattern in that lead may have been the result of transmission of the potential variations of the left ventricular cavity through the mitral orifice to the left arm, as discussed elsewhere.[29] The downward portion of the QRS in Lead aV_L was carried over as a Q wave into Lead I. Hence, no pathologic significance was attached to the findings in Lead I, and the standard leads were considered nondiagnostic of infarction.

Pathologic Findings.—The heart weighed 255 grams. A completely healed infarct was found in the subendocardial one-half of the anteroseptal wall. The infarct extended from the apex for a distance of 5.0 cm. toward the aorta and attained a maximal breadth of 3.0 cm. near the upper margin. The lateral and posterior walls were not involved. Thus, the position of the infarct was comparable to that of Case 2 (Fig. 4). An infarction limited to the subendocardial portion of the anteroseptal wall could adequately account for the abnormal Q waves in Leads V_2 and V_4, but does not ordinarily produce Q waves in V_5 and V_6. Since there was no evidence of lateral infarction to account for the Q waves in Leads V_5 and V_6, it is possible that there was sufficient rotation of the vertically placed heart to permit transmission of the potential variations of the anteroapical aspect of the left ventricle to the axilla. The infarct did not appear to extend sufficiently through the anteroseptal wall or into the septum to explain adequately the QS pattern in Leads V_1 and V_2.

CASE 14.—A man, 55 years of age, was admitted in uremic coma, secondary to prostatism. Although no history of cardiovascular disease could be obtained, a total of 1.6 mg. Cedilanid was administered during the first few hours because of the presence of cardiac enlargement and pulmonary edema. With the relief of the prostatic obstruction, the blood urea fell from an admission level of 360 mg. per cent to normal, but death from multiple renal abscesses occurred on the twenty-second hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained twenty-two hours after admission is reproduced in Fig. 15,*B*. Lead V_1 exhibited a distinct R and R′ deflection, each 2.0 to 3.0 mm. in amplitude and separated by a deep S wave. The R′ was most likely derived from activation of the conus pulmonalis. In Lead V_2 the R and downstroke of the S were similar to those of V_1, but the R′ deflection was replaced by slurring on the upstroke of the S wave. In Lead V_3 there was an initial Q wave, ranging from 1.0 to 3.0 mm. in depth, followed by an upright deflection, which exhibited considerable respiratory variation. In some cycles, as in that illustrated, it merely rose to the isoelectric line to form a notch on the descending limb of the Q wave, whereas in others it extended above the isoelectric line for a distance of 1.0 to 4.0 mm. to form an R wave. The succeeding downward component was two or more times the amplitude of the upright deflection. Lead V_4 displayed an initial Q wave, ranging from 0.5 to 2.0 mm.; an R wave, averaging 12 mm.; and an S wave, averaging 8.0 mm. in amplitude. If all of the cycles in Lead V_3 were like that illustrated, a definite diagnosis of anteroseptal myocardial infarction could have been made from the electrocardiogram. In view of the marked respiratory variations in this lead, a presumptive diagnosis was all that was justified. The downward bowing of the RS-T segment was attributed to Cedilanid. There was no evidence in either the RS-T segment or T wave to suggest recent infarction. The standard leads were not diagnostic of infarction.

Pathologic Findings.—The heart weighed 460 grams and exhibited slight left ventricular hypertrophy. An old, completely healed infarct was found in the subendocardial one-third of the anteroseptal aspect of the apical three segments, as outlined in Fig. 16. The QRS pattern in Lead V_3 was presumably a manifestation of this subendocardial infarct. Nevertheless, when marked respiratory fluctuations in the contour of QRS are present, caution must be exercised in making diagnostic inferences from the electrocardiogram. This is illustrated by a case to be reported in detail in a future communication. The tracings in this case exhibited a prominent R and deep S wave in Leads V_1 and V_2 and an initial Q wave in V_4 ranging from 2.0 to 5.0 mm. in depth and followed by an upright deflection which varied from a notch on the descending limb of the Q wave to an R wave 10 mm. in amplitude. Autopsy in this case revealed left and right ventricular hypertrophy, but no evidence of infarction.

CASE 15.—A man, 72 years of age, gave a history of repeated episodes of cardiac failure during the preceding three years, but denied thoracic pain. He was admitted in congestive failure and was digitalized, but died of bronchopneumonia on the fifth hospital day.

Fig. 16.—Roentgenogram of the injected heart of Case 14 with old healed subendocardial anteroseptal infarct outlined in black.

Electrocardiographic Findings.—An electrocardiogram obtained on the day of death is illustrated in Fig. 15,*C*. Auricular fibrillation was present. The initial deflection in Lead V_4 was consistently downward. A notched QS complex was present in V_4 in some cycles, while a small terminal R wave 1.0 to 2.0 mm. in amplitude was detectable in others. The Q wave in Lead V_4 was considered significant of anteroseptal infarction, in view of the distinct initial R wave in Leads V_1 and V_2 and the decreasing amplitude of the initial R wave in Lead V_3. The Q waves in Leads V_5, V_6, and aV_F were .02 second in duration and measured 10 to 15 per cent of the succeeding R and thus were compatible with left ventricular hypertrophy and were not sufficiently prolonged nor deep to be diagnostic of infarction. The RS-T depression in these leads was attributable to Cedilanid. The anteroseptal infarct was presumably old, since there were no characteristic T-wave changes of a recent lesion. The standard leads were abnormal, but were not diagnostic of infarction.

Pathologic Findings.—The heart weighed 654 grams and exhibited marked left ventricular hypertrophy and moderate secondary right ventricular hypertrophy. A patchy healed infarct was found localized in the subendocardial one-half of the anteroseptal wall of the left ventricle in the apical three segments, occupying the same position in the first two segments as that of Case 14 (Fig. 16) and involving the third segment in essentially the same manner as the second segment of Fig. 16. This infarct was probably responsible for the reduced R wave in Lead V_3 and the QS in V_4, but did not extend as far through the wall as would have been anticipated from

the findings in V_4. In view of the moderate clockwise rotation associated with the semivertical position, it is possible that the potential variations of the infarcted anteroapical wall might have been referred to the axilla and might have contributed to the Q waves in Leads V_5 and V_6. In the basilar one-half of the posterior wall of the left ventricle, there was a patchy fibrosis involving chiefly the subepicardial layer of muscle, but extending into the mid-zone, which was attributed to a separate infarct. When the electrocardiogram was reviewed in the light of the pathologic findings, it was concluded that the Q wave in Lead aV_F was too small and too brief in duration to justify the diagnosis of the posterior infarct found at autopsy.

CASE 16.—A man, 77 years of age, was admitted, moribund, in congestive heart failure complicated by bronchopneumonia and died thirty-four hours later. Past history was not obtainable.

Electrocardiographic Findings.—An electrocardiogram obtained after administration of 1.6 mg. Cedilanid is reproduced in Fig. 15,*D*. Auricular fibrillation was present. An initial R wave 1.0 to 2.0 mm. in height was recorded in Leads V_1 and V_2 and showed an abnormal decrease to 0.5 mm. in V_3. Lead V_4 displayed a Q wave followed by an upstroke which usually did not reach the isoelectric line, but in approximately one cycle of six, extended 1.0 mm. above the isoelectric line. Subsequent to this there was a deep downstroke, so that the complete complex in Lead V_4 consisted of a notched QS in most cycles and a triphasic QRS in occasional cycles. Since all cycles, including those with an R wave, displayed an abnormal Q pattern, a definite diagnosis of anteroseptal infarction was made from the electrocardiogram. The Q waves in Leads V_5 and V_6 were briefer in duration and smaller in proportion to the associated R waves than those of Case 15 and were not diagnostic of infarction. The changes in the RS-T segment and T wave were attributed to the Cedilanid. The standard leads were abnormal, but showed no characteristic signs of infarction.

Pathologic Findings.—The heart weighed 373 grams. Gross examination revealed an old, healed, well-vascularized anteroapical infarction almost identical in size and position to the anteroseptal portion of the infarct of Case 19 (Fig. 18). The infarct was confined to the subendocardial one-third at the apex, but extended through the subendocardial three-fourths of the anterior wall above the apex. Thus, there was close correspondence between the leads with QRS abnormalities and the position of the infarct at autopsy and rough correlation between the QRS pattern in these leads (V_3 and V_4) and the distribution of the infarct within the wall.

CASE 17.—A woman, 78 years of age, was admitted because of intestinal obstruction. She had had mild hypertension and moderate exertional dyspnea for a number of years, but gave no definite history of angina pectoris or myocardial infarction. Death occurred from peritonitis on the thirteenth hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained on the second hospital day before cardiac glycosides were given is reproduced in Fig. 15,*E*. Auricular fibrillation was present. In Leads V_1 and V_2 there was an initial R wave 2.0 mm. in amplitude, and in Lead V_3 there was a definite though smaller R wave ranging from 0.5 to 1.0 mm. in height. In Lead V_4 there was a broad, deep Q wave, slurred on its descending limb and coarsely notched on its ascending limb. In a few cycles this notch extended slightly above the isoelectric line to form a late R wave. A prominent Q wave was also found in Lead V_5 which measured approximately .04 second in duration and ranged from 40 to 66 per cent of the amplitude of the succeeding R. A minute, insignificant Q wave was visible in Lead V_6. In view of the abnormal Q pattern in Leads V_4 and V_5, a diagnosis of infarction of the anteroseptal and anterolateral aspects of the apex was made. The RS-T junction was elevated in Lead V_4 and the terminal portion of the T wave was inverted. Since serial electrocardiograms were not obtained, the question as to whether this represented a recent organizing infarct or a fixed residue of an old infarct was left unanswered. The standard leads were abnormal, but were not diagnostic of infarction.

Pathologic Findings.—The heart weighed 334 grams. A completely healed, patchy transmural infarct was found, occupying the anteroseptal aspect of the apex and extending slightly into the subendocardial layer of the lateral aspect of the apex. The position was comparable to

that of Case 14 (Fig. 16), except that this infarct extended through the entire thickness of the anteroseptal wall in the two apical segments and extended subendocardially into the lateral aspect of the left ventricle in both of these segments. Thus, there was good correlation between the electrocardiographic and autopsy findings. Since there was an abnormal Q pattern in Lead V_5 and since the infarct at autopsy extended slightly into the lateral aspect of the ventricle, this was not, in the strict sense of the definition, an anteroseptal infarct. It has been included among cases of anteroseptal infarction for purposes of contrast.

CASE 18.—A man, 60 years of age, was admitted because of a sudden onset of aphasia, which proved to be the result of cerebral embolism secondary to auricular fibrillation. Past history was unobtainable. The patient died on the twenty-second hospital day of peritonitis from ruptured empyema of the gall bladder.

Electrocardiographic Findings.—An electrocardiogram obtained on the fourth hospital day after a total of 0.9 Gm. of digitalis is reproduced in Fig. 15, *F*. An R wave 2.0 to 3.0 mm. in amplitude was present in Leads V_1 and V_2 and a smaller but definite R wave was easily made out in V_3. In most of the cycles in Lead V_4 a QS complex was present, but in a few, a minute initial R wave 0.5 mm. in amplitude was detectable. In all cycles there was splintering of the apex of the downward deflection. An initial Q wave, which was relatively small in proportion to the succeeding R wave, was present in Leads V_5, V_6, and aV_F. The progressive diminution in the R wave as the electrode was moved from Position C_1 to C_4 was strongly suggestive of small anteroseptal infarction, localized near the apex, but was also compatible with right ventricular dilatation. The fact that the T waves were sharply inverted in Leads V_3 and V_4 and flattened in V_1 pointed toward the former, but positive diagnostic inferences were unwarranted because of rather typical digitalis effects in Lead V_6. Since further tracings failed to reveal the expected serial changes, a final ante-mortem interpretation was made of an old, healed, patchy anteroseptal infarct in the apical region. The standard leads were abnormal, but were not diagnostic of anteroseptal infarction.

Pathologic Findings.—The heart weighed 444 grams and showed moderate left ventricular hypertrophy. There was no evidence of right ventricular dilatation or pericarditis. An old, completely healed infarct was found in the anteroseptal wall of the apical two segments in a position similar to that of Case 14 (Fig. 16). A patchy transmural lesion was found in the apical segment, and the subendocardial one-third was involved in the second segment. In addition, the infarct in this case extended around the tip of the left ventricle to involve the posterior aspect of the apical two segments. Thus, the abnormal QRS pattern in Leads V_3 and V_4 was apparently a manifestation of the infarction of the anteroseptal portion of the apex found at autopsy. However, the somewhat larger infarct of the posterior wall of the apex was not clearly revealed by the electrocardiogram.

CASE 19.—A man, 47 years of age, began to have angina pectoris in the summer of 1943. On Oct. 8, 1943, he was awakened by severe protracted retrosternal oppression, and on October 22 he had a second similar attack. Since that time he had occasional attacks of angina pectoris, but no further episodes of protracted retrosternal pain. He dropped dead from exertion immediately after dinner on Nov. 3, 1944. No cardiac glycosides were given during the entire period of observation.

Electrocardiographic Findings.—Electrocardiograms selected from a series taken over a period of one year are reproduced in Fig. 17. In the first tracing of Sept. 3, 1943, taken before exercise, the initial phase of the QRS and the T wave were upright in all precordial leads and there was a progressive increase in the ratio of R to S wave as the electrode was moved from Position C_1 toward the left. In the second curve, taken on the same day immediately after exercise, there was no significant change in QRS, but the T wave became sharply inverted in Leads V_1, V_2, V_3, and V_4 and the RS-T junction dropped below the isoelectric line in Leads V_5 and V_6. This change was interpreted as evidence of ischemia of the anteroseptal wall of the left ventricle. The RS-T junction was depressed in Leads II and III; T_2 was diphasic; T_3 was inverted in the resting electrocardiogram and showed no significant change after exercise. The

tracing on October 8 was obtained eleven hours after the onset of the protracted retrosternal oppression. A small but distinct R wave was detectable in Lead V_1 similar to that present in previous tracings, but a QS complex was consistently present in Leads V_2 and V_3. The RS-T junction was slightly elevated in Leads V_1, V_2, and V_3 and the T wave was sharply inverted. These changes were indicative of a recent anteroseptal infarction. The QRS complex in Leads

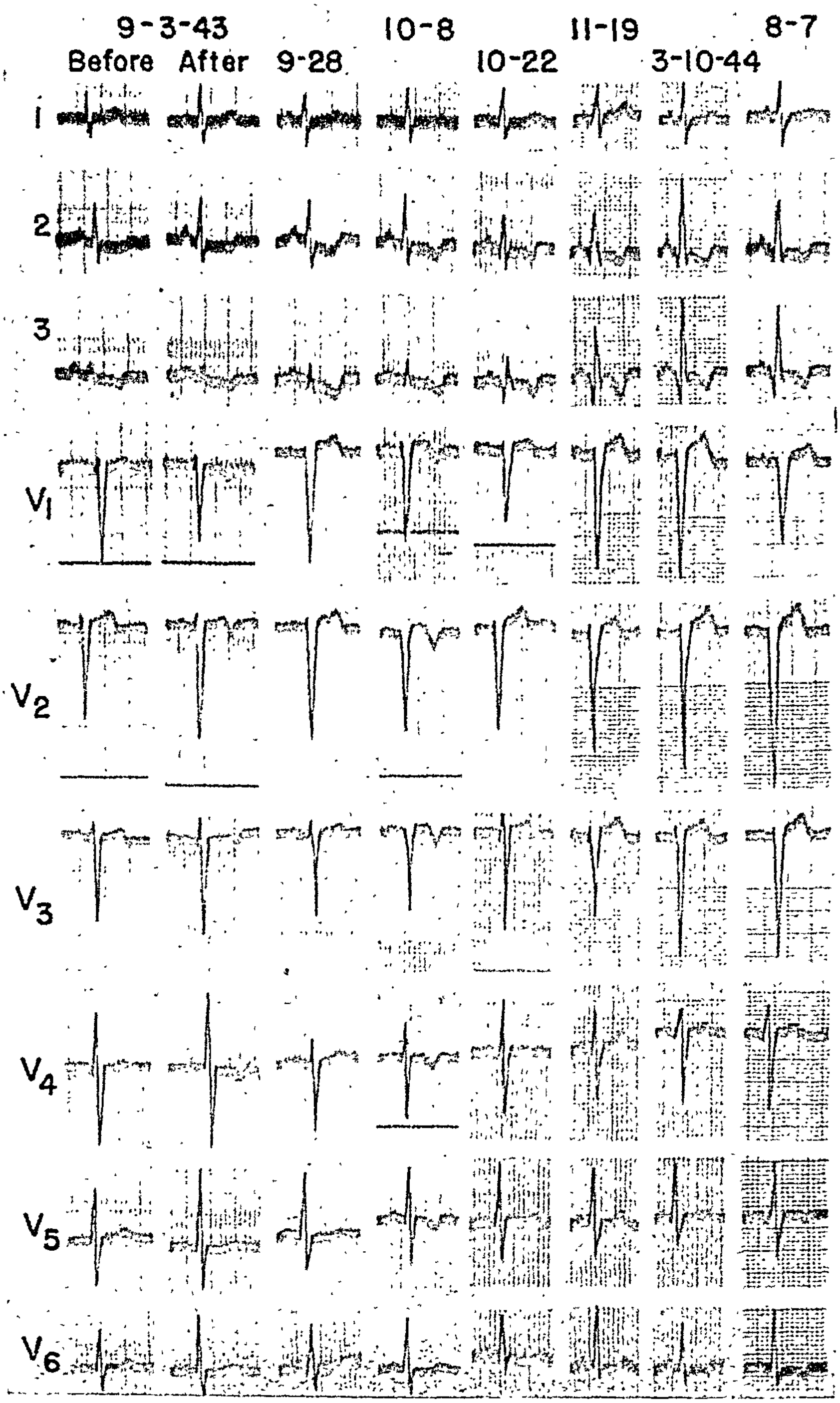

Fig. 17.—Serial electrocardiograms of Case 19, showing acute inversion of the T waves in the first precordial lead after exercise on September 3, anteroseptal infarction on October 8, and posterior infarction on October 22.

V_4, V_5, and V_6 showed no significant change, but the inversion of the T wave in Leads V_4 and V_5 was probably representative of an outlying zone of ischemia. By October 22 the QRS-T pattern in the precordial leads again resembled that in the initial tracing of September 3. It is noteworthy that a distinct R wave had reappeared in Leads V_2 and V_3 and, though abnormally small, was detectable in these leads in all subsequent tracings. Thereafter, the T wave in Leads V_1, V_2, and V_3 was consistently upright and fairly uniform in configuration, but that in Leads V_4, V_5, and V_6 varied in direction and amplitude. On October 22 a definite Q wave first appeared in Leads II and III and persisted in these leads, as well as in Lead aV_F, in the remainder of his tracings. The appearance of the Q wave in Leads II and III on October 22, together with the unusually rapid disappearance of the changes in Leads V_2 and V_3, was attributed to infarction of the posterior wall of the left ventricle.

Pathologic Findings.—The heart weighed 523 grams and exhibited left ventricular hypertrophy. Gross and microscopic examination revealed a well-vascularized infarct, involving the subendocardial one-half of the anteroseptal wall of the left ventricle, extending from the apex halfway toward the base. This infarct was continuous through the septum, with a larger healed subendocardial infarct involving the entire posterobasal portion of the left ventricle, as indicated in Fig. 18. The anteroseptal infarct found at autopsy confirmed the diagnosis made on

Fig. 18.—Roentgenogram of the injected heart of Case 19.

October 8, but extended farther toward the apex than had been postulated from the tracing. The posterior infarct was larger than had been anticipated from the tracing of October 22 and subsequent electrocardiograms. The records of Sept. 3, 1943, showed that ischemia of the anterior wall had preceded the infarction. Whether the RS-T depression and the T-wave inversion

in Leads II and III prior to October 22 were due to ischemia or to antecedent subendocardial infarction of the posterior wall remains in doubt.

CASE 20.—A man, 80 years of age, had an attack of prolonged retrosternal pain radiating to the back on Jan. 25, 1946, and was admitted three days later because of residual oppression. The patient was in good clinical condition on admission and remained so until 4:00 P.M. on January 29 when the retrosternal pain recurred, followed by shock and loss of consciousness. He failed to rally and died on February 2.

Electrocardiographic Findings.—An electrocardiogram taken on January 28, three days after the onset of the first attack of retrosternal pain and before the administiation of cardiac glycosides, is reproduced in Fig. 19, together with a second tracing taken on January 30, twenty-two hours after the onset of the second attack of pain and after the administration of 0.8 mg. of Cedilanid. Leads V_1, V_2, and V_3 of the tracing of January 28 revealed a QS complex and a markedly elevated RS-T take-cff typical of the central zonal pattern in the stage of injury. Lead V_4 displayed a small Q, a relatively tall R, and elevated RS-T junction, indicating a marginal zonal pattern. Since Leads V_5 and V_6 of the tracing showed no QRS abnormalities, a diagnosis was made of a recent infarct limited to the anteroseptal wall of the left ventricle and the adjacent anterior portion of the septum. The T pattern of V_4 was referred to the left arm and thus appeared in Lead I. It is noteworthy that Lead aV_F showed a fairly well developed initial R wave and a reciprocal RS-T depression, which carried over into Leads II and III. In the tracing of January 30 the appearance of a deep Q wave, a markedly reduced R wave, and an elevated RS-T junction in Leads V_4, V_5, and V_6 signified extension of the infarct into the lateral aspect of the apex, and the development of a W-shaped QRS in Lead aV_F indicated extension into the posterior aspect of the apex. The pattern in the standard leads of January 30 was also compatible with an anteroposterior infarct.

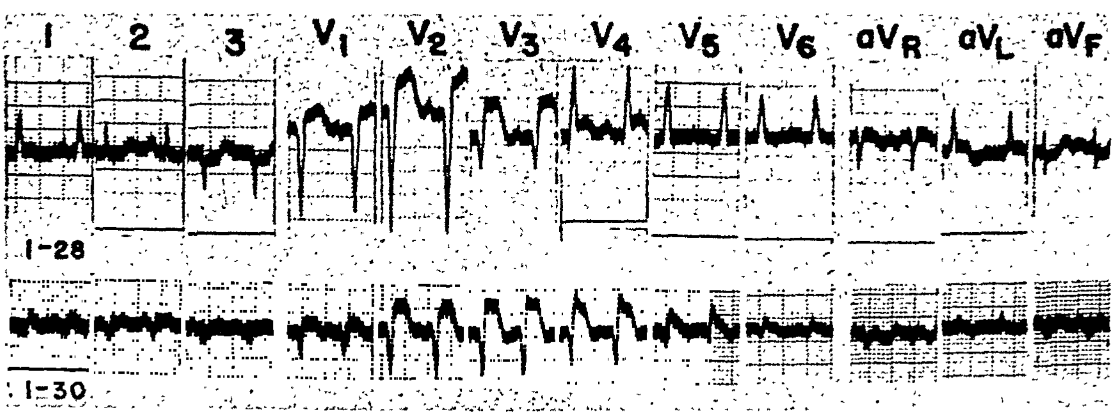

Fig. 19.—Electrocardiograms of Case 20, showing anteroseptal infarct on January 28 with extension to lateral and posterior aspects of apex on January 30.

Pathologic Findings.—The heart weighed 532 grams and exhibited left ventricular hypertrophy. There was a recent infarct, involving the left one-half of the septum and adjoining anteroseptal wall of the left ventricle, which had extended into the lateral and posterior walls of the apex, as outlined in Fig. 20. A terminal slitlike rupture had occurred at the junction of the anterior wall and septum in the third segment from the apex. The microscopic findings were in keeping with the electrocardiographic diagnosis of a recent anteroseptal infarct which had subsequently extended into the lateral and posterior walls of the apex.

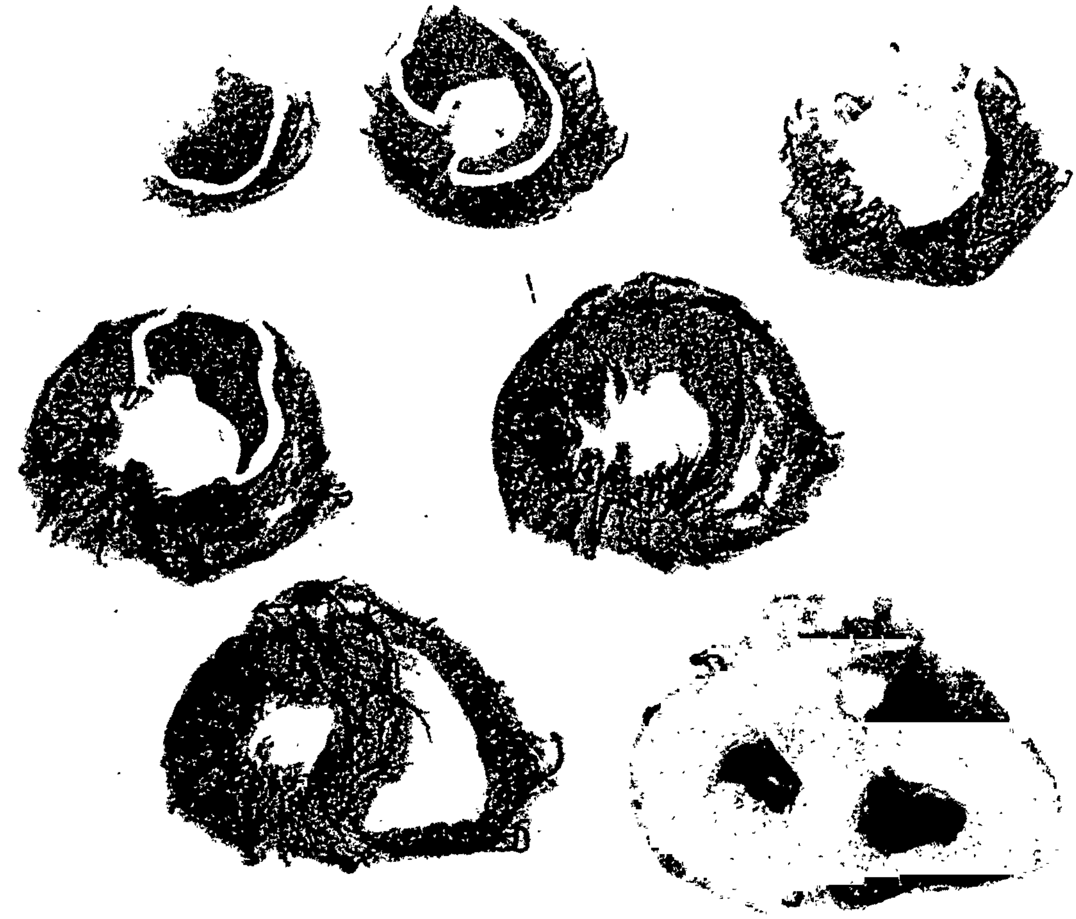

Fig. 20.—Roentgenogram of the injected heart of Case 20.

COMMENT

Electrocardiographic Signs of Anteroseptal Infarction.—The various patterns associated with anteroseptal infarction have been illustrated and discussed in the individual case reports and will be classified and summarized in this section. In general, the observations in this series of cases confirm and amplify the reports of Wilson and associates.[18,19,25]

Classical QRS Pattern in Anteroseptal Infarction.—This pattern is characterized by (1) presence of a normal initial R in Lead V_1 or in another lead from the right anterior chest wall; (2) replacement of the normal initial upright deflection in one or more of the next three leads (V_2, V_3, V_4) by a QS or an abnormal QR complex; and (3) absence of an abnormal Q wave from Leads V_5, V_6, and aV_L and the standard limb leads. The Q wave of a QR complex is considered abnormal when the time interval from its onset to nadir exceeds .02 second and when its amplitude is more than 25 per cent of the voltage of the succeeding R in every cycle. The entire lead should be examined to make sure that the abnormality in the initial phase of the QRS is present in every cycle, since marked respiratory fluctuations between an initial downward and an initial upward deflection may occasionally be observed in a lead at the transitional zone in the absence of myocardial infarction. A consistently abnormal

QR or QS deflection localized to Leads V_2, V_3, and/or V_4 is virtually diagnostic of anteroseptal infarction, particularly when Lead V_1 displays a normal RS complex consisting of a small, brief, initial upright deflection, averaging 2.0 to 3.0 mm. in amplitude and .01 to .02 second in duration, followed by a much larger and broader downward deflection. The presence of a QS deflection in Lead V_1 as well as in V_2 constitutes an indication for at least two additional leads from the right precordium, preferably V_{3R} and V_E. When an RS complex with normal initial upright deflection can be found in one or more of these leads, the QS in Leads V_1, and V_2 is, in all probability, the result of anteroseptal infarction. The qualification of the foregoing patterns, as practically diagnostic, rather than as pathognomonic, of anteroseptal infarction is necessitated for two reasons: (a) infarction localized to the lateral wall of the left ventricle may lead to abnormal Q waves in Leads V_2, V_3, and V_4 when there is sufficient counterclockwise rotation of the heart to cause transmission of the potential variations of the lateral wall to the precordium (this will be exemplified and discussed further in a subsequent manuscript on lateral infarction); (b) in uncomplicated right ventricular dilatation and hypertrophy,[30] a normal RS complex may be recorded in Lead V_1 and reduction or even disappearance of the initial R wave may occur in a transitional lead farther to the left. Since full consideration of the differentiation of the electrocardiographic findings in anteroseptal infarction from those in right ventricular dilatation and hypertrophy and from other patterns which may be confused, such as those of uncomplicated bundle branch block, left ventricular dilatation and hypertrophy, and pericarditis, would require a number of additional illustrations, it has been reserved as a subject for a separate communication.

Classical RST-T Pattern in Anteroseptal Infarction.—The findings in leads with an abnormal Q wave and/or abnormal reduction of the R wave depend upon the age of the infarction. Early in the stage of injury associated with a very recent infarction, the RS-T junction is elevated 2.0 to 8.0 mm. or more above the isoelectric line. The RS-T segment ascends to a peak in a straight line or a curved line with upward convexity (instead of the normal upward concavity) and the T wave returns precipitously to the isoelectric line, thereby completing a monophasic upright RST-T complex, as illustrated in Leads V_2, V_3, and V_4 of Cases 8 and 9. The RS-T displacement soon begins to recede and the terminal portion of the T wave starts to dip below the isoelectric line. As the RS-T junction approaches the isoelectric line, the T wave becomes more and more deeply inverted and takes on a characteristic cove plane contour. The RS-T segment begins at a point above or on the isoelectric line (but not actually depressed) and ascends in an arc with upward convexity to reach a level above the RS-T junction and then curves sharply downward to form an inverted V-shaped T wave with pointed apex and steep descending and ascending limbs. After reaching a maximal depth, the T wave gradually recedes. As it diminishes in depth, the gradient of the proximal and distal limbs becomes less and less steep, making the apex more and more rounded. The RS-T junction usually remains isoelectric or very slightly elevated and the RS-T segment generally retains its dome-shaped contour for a considerable time. Eventually

the T wave may become flat and finally may become upright and normal in contour. The foregoing classical evolution in the RST-T complex is illustrated in Lead V_2 of Case 2 (Fig. 3). However, stabilization may occur at any stage of the evolution. Thus, in some cases, the characteristic cove plane inversion of the T wave may remain permanently and in a few cases the upwardly displaced RS-T segment and monophasic upright T wave may persist indefinitely.

The combination of abnormal Q waves localized to Leads V_2, V_3, and V_4 with classical changes in the RST-T complex which has been described is pathognomonic of infarction and may be attributed to a localized anteroseptal infarct, provided there is no unusual degree of cardiac displacement or rotation. Isolated changes in the RS-T segment and T wave, resembling those just decribed, may occur in acute right ventricular dilatation and in pericarditis and consequently are not diagnostic of anteroseptal infarction. Their differentiation has been considered in the case discussions and will be elaborated upon in a subsequent communication.

In acute anteroseptal infarction, sharply inverted T waves may be recorded in Leads V_5 and V_6, whence they are transmitted to the left arm and registered in Leads aV_L and I. T waves of this description, when unaccompanied by an abnormal Q wave or abnormal reduction in the R wave, are a manifestation of an outlying ischemic zone and usually undergo a rather rapid evolution with return to normal or to a pattern more in keeping with underlying left ventricular hypertrophy.

Variants in the QRS Pattern in Leads V_1, V_2, V_3, and V_4.—The classical pattern which has just been described is not present in every case of anteroseptal infarction. It was found in seven of the twenty cases comprising this series (Cases 3, 6, 7, 15, 16, 17, and 19). In Case 19 the QS complexes localized to Leads V_2 and V_3 were very transient and initial R waves reappeared in these leads concomitantly with extension of the infarct into the posterior aspect of the left ventricle. In one additional case (Case 14) the QRS abnormalities were localized to Lead V_3 and were considered typical in some but not in all cycles due to modification from respiratory influences on cardiac position. The deviations from the classical QRS pattern in the first four precordial leads of the remaining cases could be classified into the following five categories:

1. Abnormal decrease in the amplitude of the initial R wave without complete disappearance of this deflection as the electrode was moved to the left from Position C_1 or C_2. This is exemplified by the electrocardiogram of Case 18, in which a 2.0 to 3.0 mm. initial R wave was found in Leads V_1, and V_2, a 1.0 mm. R wave in V_3, and an 0.5 mm. initial R wave in some cycles of V_4. Such a pattern may also occur in uncomplicated right ventricular dilatation and in right ventricular dilatation and hypertrophy. The differential diagnosis was considered in the discussion of Case 18.

2. A small but definite Q wave preceding an RS complex in Lead V_1 or in Leads V_1 and V_2. This is illustrated by Lead V_1 of Case 5, which displayed an 0.5 mm. Q wave followed by a 1.5 mm. R wave and a 10 mm. S wave. An initial Q wave preceding such an RS complex in Lead V_1 or in V_1 and V_2 is

abnormal and indicative of infarction of the interventricular septum, as will be further exemplified and discussed in a subsequent manuscript on that subject. A combination of this finding in Lead V_1 or in V_1 and V_2 with an abnormal QS or QR complex in Lead V_3 or in V_3 and V_4 is diagnostic of anteroseptal infarction.

3. The presence of a QS complex in Leads V_1 and V_2 or in V_1, V_2, and V_3. A QS complex was found in these leads in five cases of this series (Cases 2, 8, 9, 13, and 20) and was limited to Lead V_1 and to leads from the right anterior chest wall in three additional cases (Cases 1, 11, and 12). When an RS complex with normal initial R wave is not demonstrable in leads from the right side of the chest, a decision as to whether a QS complex in Leads V_1, and V_2 is due to anteroseptal infarction or to other causes, such as backward rotation of the apex,[21] will depend upon the QRS pattern in Leads V_3 and V_4 and the RST-T contour in the first four precordial leads. For example: in the antemortem interpretation of the electrocardiogram of Case 13, the QS of Leads V_1 and V_2 was attributed to anteroseptal infarction because of the presence of an abnormal QR complex in V_3 and V_4; in Case 9 the QS complexes of Leads V_1, V_2, and V_3 were evidently due to recent anteroseptal infarction because of the typical RST-T pattern in the same leads. Abnormal QS complexes in Leads V_1 and V_2 tend to occur as a result of extension of the infarct into the septum and are attributable to reduction or obliteration of the positive potentials ordinarily referred to the right side of the precordium during activation of the septum. When the infarct is confined to the basilar portion of the septum, as in Cases 11 and 12, the QS complexes and "coronary" T waves may be localized to Leads V_1 and V_{3R}. The QS complex limited to V_1 of Case 1 could be attributed to high anteroseptal infarction because of its observed development in serial tracings along with rather typical changes in the RS-T segment and T wave.

4. Right bundle branch block, characterized by the presence of a Q wave in place of the customary initial R wave in leads from the right side of the precordium. This may occur as a result of extension of an anterior infarct into the septum. Our cases of anterior septal infarction with right bundle branch block will be reported in a communication on septal infarction.

5. Absence of diagnostic abnormalities in the QRS complexes of the first four precordial leads. Serial changes in the T waves without significant QRS abnormalities in the first four precordial leads were observed in Cases 4 and 69 (to be reported later) during the acute stage of a small anteroseptal infarct, which subsequently proved to be intramural in location. Thus QRS abnormalities may be absent when the infarct is small and confined to the mid-zone of the myocardium (that is, when both the subendocardial and subepicardial layers are spared). Marked RS-T displacement without significant abnormalities in the initial phase of the QRS complex were observed in Case 10 in which autopsy revealed a considerably larger but patchily distributed infarct in the apical one-half of the anteroseptal wall. The absence of a Q wave in this case may have been due to the patchy character of the infarct.

Variants in the QRS Pattern in Leads V_5 and V_6.—Abnormal Q waves are characteristically absent from Leads V_5 and V_6 when the infarct is confined to the anteroseptal portion of the left ventricle. Their presence in these leads is usually the result of infarction of the anterolateral or lateral aspect of the apex, as exemplified by Cases 17 and 20. In the latter case, the extension of an anteroseptal infarct into the lateral wall was manifested by replacement of the normal initial R wave originally present in Leads V_5 and V_6 by an abnormal QR complex. When the heart is rotated clockwise on its longitudinal and anteroposterior axes, the potential variations of the epicardial surface of an infarct confined to the anteroseptal wall may be referred to the axilla and give rise to borderline or abnormal QR complexes in Leads V_5 and V_6, as in Cases 13 and 15. Under these circumstances, however, deeper, broader Q waves are recorded in Leads V_3 and V_4 than in V_5 and V_6. The distribution of the Q waves resulting from anteroseptal infarction differs significantly from the sites of predilection for the normal Q waves in left ventricular leads. The normal Q is deeper and broader in Lead V_6 than in V_5 and further diminishes or disappears in Lead V_4.

Variants in the QRS Pattern in the Standard Leads and in aV_L.—The well-known inadequacy of the standard limb leads in the detection of anteroseptal infarction was borne out by lack of diagnostic signs in these leads in eighteen of the twenty cases in this series. In the two remaining cases (Cases 8 and 20) there was RS-T elevation in Lead I and reciprocal depression in Lead III, which was strongly suggestive of recent anterior infarction. This was due to a cardiac position which favored transmission along a pathway from the C_3 or C_4 precordial position to the left arm in place of the more common pathway from axilla to left arm. This was evident from the resemblance of the pattern in Lead aV_L to that in V_3 of Case 8 and from the similarity of the findings in Lead aV_L to those of V_4 in the tracing of January 28 of Case 20. Thus, Leads aV_L and I may occasionally show diagnostic signs when the infarct is limited to the anteroseptal area.

Correlation of Electrocardiographic and Pathologic Findings.—This has been discussed in some detail in connection with each individual case report and will be summarized in this section. Wilson and associates[13-17] succeeded in demarcating the precise boundaries of experimental infarcts in animals through the use of multiple direct leads from the exposed epicardium. A similar degree of accuracy in the determination of the size and position of human myocardial infarcts cannot be achieved with multiple precordial leads, for obvious reasons: (1) A precordial lead is dominated by the potential variations of a much larger segment of myocardium than a direct lead and when situated at the border of the infarct will register an admixture of effects from the infarcted and outlying areas. (2) The anatomic relation of the heart to fixed points on the chest wall is subject to considerable variation among different individuals, because of differences in the size and position of the heart. This interjects an element of uncertainty in the prediction of the portion of the heart involved by a lesion responsible for a localized abnormality in the precordial leads. Furthermore,

Wilson and associates were able to demonstrate a close correspondence between the QRS pattern in a direct epicardial lead and the distribution of the infarct through the subjacent segment of myocardium. A similar degree of accuracy could not be attained with precordial leads unless the infarct is uniform in distribution throughout the entire segment of myocardium subtended by the electrode. In view of the foregoing considerations, it becomes of interest to correlate the findings in the precordial leads, which serve as an estimate of the surface area and location of the lesion and the proportion of the wall infarcted with the anatomic findings at autopsy.

Correlation Between the Leads Exhibiting Abnormal QRS Patterns and the Size and Position of the Infarct at Autopsy.—Extension of the infarct into the anterior portion of the interventricular septum was found at autopsy in thirteen cases of this series. An abnormal initial downward deflection was demonstrated in right ventricular Leads V_1 and V_2 or in V_1 and V_{3R} in seven of these cases (Cases 2, 5, 8, 9, 11, 12, and 20). For reasons already given, this initial downward deflection was ascribed to obliteration of the initial positive potentials ordinarily referred to the right precordium during septal activation and was therefore regarded as evidence of extension of the infarct into the septum. In the remaining six cases (Cases 3, 4, 7, 10, 16, and 19) Lead V_1 or V_1 and V_2 displayed an RS complex, which was not diagnostic of septal infarction. The septal involvement was patchy in all six cases and the initial R may have been derived either from preserved muscle in the septum or from the activation of the free wall of the normal right ventricle. Septal extension was not demonstrated pathologically in seven cases. A normal initial R wave was found in Leads V_1 and V_2 in four of these (Cases 14, 15, 17, and 18) and in V_1 in one case (Case 6). In the two remaining cases (Cases 1 and 13), where a QS complex was recorded in V_1 or in V_1 and V_2, it is possible that a septal extension was missed pathologically through failure to take microscopic sections through the septum. Thus, extension into the septum may be revealed by an abnormal initial downward deflection in right ventricular Leads V_1 and V_2 or may occur without diagnostic signs in these leads.

The infarction of the anteroseptal portion of the outer wall was classified, according to location, into the following three groups: (a) apical one-third to two-thirds, (b) middle one-third, and (c) basal one-third.

In fourteen cases, the infarct occupied the apical one-third to two-thirds of the anteroseptal wall. In one of these cases (Case 10), a diagnostic QRS pattern was not present in any precordial lead, perhaps because of the patchy character of the infarct. Of the remaining thirteen, Lead V_4 displayed an abnormal QS or QR in nine (Cases 3, 7, 8, 13, 15, 16, 17, 18, and 20) and an abnormal marginal zonal RS complex in one (Case 9). In Case 2, Lead V_4 displayed an ischemic zonal pattern in the early tracings and a marginal zonal pattern in the later tracings. The absence of diagnostic signs in Lead V_4 of the apical infarct found at autopsy in the two remaining cases (Cases 14 and 19) may have been due to a cardiac position which facilitated transmission of potential variations of the apex to a point medial to the mid-clavicular line. Lead

V_3 exhibited an abnormal QS or QR complex in ten of the fourteen cases and an abnormal RS of marginal zonal type in three (Cases 16, 17, and 18). An abnormal initial downward deflection was found in Lead V_2 in seven cases, but may have been referable to the associated involvement of the septum rather than the lesion in the outer wall. Leads V_5 and V_6 did not show a definitely abnormal initial downward deflection in any case where the infarct was confined to the anteroseptal wall. Borderline QR complexes were found in these leads in two cases where there was moderate clockwise rotation of the heart on its longitudinal and anteroposterior axes, and definitely abnormal QR complexes might result from more marked clockwise rotation. Thus, in general, there was good correlation between QRS abnormalities in Leads V_3, and V_4 and infarction of the apical one-third to two-thirds of the anteroseptal wall. However, accurate determinations of size and distinction between infarcts involving the apical one-third and the apical two-thirds of the anteroseptal wall could not be made from the findings in Leads V_3 and V_4.

The infarct was centered in the mid-portion of the anteroseptal wall in two cases. In one of these (Case 6) an abnormal QR pattern in V_2 was referable to the lesion in the outer wall, inasmuch as the septum was uninvolved. Lead V_4 of this case displayed a marginal zonal pattern, despite the fact that the infarct did not quite reach the apex. In the other case (Case 4) no abnormalities were found in the initial phase of the QRS, probably because of the small size and intramural location of the infarct, but serial changes in the T wave of Leads V_2 and V_3 corresponded, in general, with the position of the infarct.

The infarct was located in the basal one-third of the anteroseptal wall in four cases (Cases 1, 5, 11, and 12). Abnormal QRS patterns were limited to Leads V_1, V_2, and V_3 of Case 5, to V_1 and V_2 of Case 1, and to V_{3R}, V_1, and V_2 of Cases 11 and 12. Since infarction of the basal portion of the interventricular septum was demonstrated in three of these cases, the question was left unsettled as to whether the QRS abnormalities were due exclusively to the infarction of the septum or partly to the involvement of the adjacent anteroseptal wall. At any rate, there was good correlation between the leads showing QRS abnormalities and the basal location of the infarct.

Correlation Between QR Relationships in the Precordial Leads and the Distribution of the Infarct in the Underlying Myocardium.—Transmural infarction, extending from endocardium to epicardium, was demonstrated pathologically in thirteen of the cases. A QS complex was recorded in at least one lead of twelve of these cases. Notching or slurring of the QS deflection was present in the majority and could usually be correlated with preservation of islands of muscle in the infarcted area. The infarct was limited to the subendocardial one-half to two-thirds of the wall in six cases. A QS complex was present in at least one lead of all of these cases. In Case 19 the QS was a transient phenomenon during the acute stage and in Case 14 it exhibited respiratory metamorphosis to a QRS. The QS was notched in Cases 5, 15, and 16 and was accompanied by an intermittent late R in the latter two. In the remaining case

(Case 13) the QS was limited to Leads V_1 and V_2 and could not be satisfactorily correlated with the autopsy findings. Intramural infarcts limited to the mid-portion of the wall were found in Case 4 and in Case 69, to be reported later. These were manifested by serial changes in T waves without definite abnormalities in QRS. In general, there appeared to be a rough correlation between the QR relationships in the precordial leads and the distribution of the infarct between the endocardium and epicardium of the underlying wall; however, notched or slurred QS complexes, resembling those associated with transmural infarction, were found in cases where the infarct was limited to the subendocardial one-half of the wall.

Correlation Between the RST-T Pattern in the Precordial Leads and the Age of the Infarct at Autopsy.—The determination of the age of the infarct was greatly facilitated by serial tracings, as exemplified by Cases 1, 2, 3, 4, 19, and 20. A diagnosis of very recent infarction, made from marked upward RS-T displacement and monophasic upright T waves in Cases 8, 9, and 10, was verified at autopsy. However, cove plane inversion of the T waves in central zonal leads was demonstrated within a few hours after the development of the infarct in Cases 6, 11, and 12. An electrocardiogram in Case 2, taken nine hours after the onset of the attack and one hour before death, showed typical signs of a terminal posterior infarction, and autopsy revealed fresh occlusion of the right corornay artery, but no gross or microscopic evidence of infarction. These findings are in accord with the experience in animals, that electrocardiographic signs precede histologic evidence of infarction.[28] The single electrocardiogram in Case 5 revealed T-wave changes suggestive of recent subendocardial infarction, but autopsy disclosed an infarct which was considerably older than had been anticipated. The contour of the inverted T waves in the first electrocardiogram taken in Case 18 was suggestive of recent infarction, but the lack of significant change in subsequent tracings indicated a stabilized pattern from old infarction. Thus, a reliable estimate of age of the infarct cannot be made from a single electrocardiogram in the absence of other clinical data.

Diagnostic and Localizing Value of a Single Precordial Lead.—In a number of cases where a positive or presumptive diagnosis of anteroseptal infarction could be made from a study of multiple precordial leads, either no evidence or equivocal signs could be elicited from a single precordial lead, regardless of the position of the electrode. For example, the pattern in Lead V_4 was not diagnostic of infarction in Cases 1, 4, 5, 10, 11, 12, 14, and 19 and would have been equivocal in several other cases if leads on either side of the mid-clavicular line had not been available. The customary Lead IV, in which the electrode is applied over the apical impulse, probably would have given even less information, since the impulse was displaced beyond the mid-clavicular line near the C_5 precordial position in a number of the cases. The RS complex in Lead V_2 was not diagnostic of infarction in Cases 3, 4, 10, 11, 12, 14, 15, 16, 17, and 18 and the significance of the QS deflection recorded in this lead in several other cases would have remained in doubt without other leads for comparative purposes. Thus, the standard leads and a single precordial lead would have been

inadequate for diagnostic purposes in the majority of the cases of this series and would have been insufficient for localizing purposes in all cases.

SUMMARY

The findings in the Wilson precordial leads and in the standard and Goldberger limb leads have been correlated with the pathologic findings in 161 cases in which myocardial infarction was definitely established and accurately localized at autopsy. The cases have been classified in accordance with the anatomic location of the infarct into the following seven groups: anteroseptal, large anterolateral, anteroposterior, septal, posterior, posterolateral, and lateral. When classification into more than one category was possible, because of the large size or multiplicity of the infarct found at autopsy, the lesion of principal electrocardiographic interest became the determining factor.

This communication comprises a study of the electrocardiographic and pathologic findings in twenty cases of anteroseptal infarction. In the majority, the infarct was confined to a relatively narrow strip of the free anterior wall and the contiguous anterior portion of the interventricular septum. Serial electrocardiograms taken during the acute phase are presented in six cases and include a control tracing antedating the infarct in four cases, and one or more records after healing in four cases. Single electrocardiograms obtained during the stage of injury are presented in eight additional cases. The remaining six cases came under study after the infarct was completely healed.

In fourteen cases, the infarct involved the apical one-third to two-thirds of the anteroseptal wall of the left ventricle. The electrocardiogram in eight of these cases was characterized by a normal initial R wave in Lead V_1 and an abnormal QR or QS complex in one or more of the next three leads (V_2, V_3, and V_4). The Q wave of a QR complex was considered abnormal when the time interval from its onset to nadir exceeded .02 second and when its amplitude was more than 25 per cent of the voltage of the succeeding R. The electrocardiogram in five of the fourteen cases displayed a QS complex in Leads V_1 and V_2, as well as an abnormal initial downward deflection in Lead V_3 or V_3 and V_4. In four of these five cases, the QS complexes in Leads V_1 and V_2 were accompanied by abnormal elevation of the RS-T segment and could be correlated with extension of the infarct into the septum. The electrocardiogram of the last case in the group displayed marked RS-T displacement in Leads V_2, V_3, and V_4 without significant abnormalities in the initial phase of the QRS complex. The registration of an R wave in place of a Q wave in these leads could be correlated with the patchy distribution of the infarct through the anteroseptal wall.

In two cases, the infarct was centered in the middle one-third of the anteroseptal wall and did not reach either the apex or base. The tracing of one of these displayed a normal initial R wave in Lead V_1 and an abnormal QR or QS complex in the next three leads. Serial changes in the T waves of Leads V_2 and V_3 without significant QRS abnormalities were observed in the other case during the acute stage of an anteroseptal infarct, which subsequently proved to be small in size and intramural in location.

The infarct was located in the basal one-third of the anteroseptal wall in the four remaining cases and was manifested by an abnormal QR or QS pattern together with abnormal RS-T displacement confined to the first two or three precordial leads. Extension of the infarct into the basal one-third of the interventricular septum was demonstrated in three of these cases and may have been partly or wholly responsible for the QRS-T abnormalities in Leads V_1 and V_2.

Definitely abnormal Q waves were not found in Leads V_5 or V_6 in any case where the infarct was confined to the anteroseptal wall, but borderline QR complexes were recorded in these leads in two cases and were attributed to reference of the potential variations of the anteroseptal infarct toward the axilla as a result of clockwise rotation of the heart on its longitudinal and anteroposterior axes.

Diagnostic signs of anterior infarction were found in the standard limb leads in only two of the twenty cases. These three leads, together with a single precordial lead, would have been inadequate for diagnostic purposes in the majority of the cases in this series and would have been insufficient for localizing purposes in all cases. On the other hand, multiple precordial leads furnished adequate evidence in all cases for a positive or presumptive diagnosis of myocardial infarction and for a clinically satisfactory prediction of the position of the lesion.

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THE EFFECT OF INTRAVENOUS PROCAINE ON THE ELECTROCARDIOGRAM OF THE DOG

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DURING the past few years the intravenous administration of procaine has been found to be useful in the treatment of an increasingly greater variety of medical conditions. Investigators have reported its administration in attempting to control tinnitus aurium,[15] severe pruritus,[16] side effects of massive doses of neoarsphenamine,[23] allergic and drug reactions,[7] serum sickness,[4,21] reactions to penicillin,[12] pain associated with extensive burns,[14] postoperative pain, [1,19] dyspnea and asthma,[11] the severe pain of frostbite,[6] and for producing obstetrical analgesia.[3] Experimentally[2,8,9,13,17,20,22,24] and clinically[5,10,18] procaine has been shown to be partially effective in decreasing or controlling the activity of ectopic pacemakers in the heart.

The specific effects of this drug on the heart as manifested by electrocardiographic changes have not been previously reported; this is the purpose of this investigation.

METHODS

Eight dogs, anesthetized with pentobarbital sodium (25 mg. per kilogram of body weight), were used for this study. Use of the barbiturate was necessary to control the powerful convulsant action of procaine. After fifteen to thirty minutes were allowed for stabilization of the anesthetic level, 50 mg. per kilogram of procaine hydrochloride (made up as 50 mg. per cubic centimeter) was administered intravenously, the duration of injection varying between 15 and 120 seconds. Electrocardiograms (Lead II) were taken before, during, and at frequent intervals after the injections, and the records were analyzed for changes in heart rate, rhythm, and contour of the deflections.

RESULTS

The most striking changes were the tendency of the P-R and the QRS intervals to prolong, leading to the development of A-V and intraventricular block (Fig. 1). These findings appeared to vary with the rate of injection; that is, the more rapid the administration, the more pronounced the change. Nevertheless, the effects were present to some degree in all experiments. Further noted were: (1) a tendency for heart rate to increase or decrease, related generally to the speed

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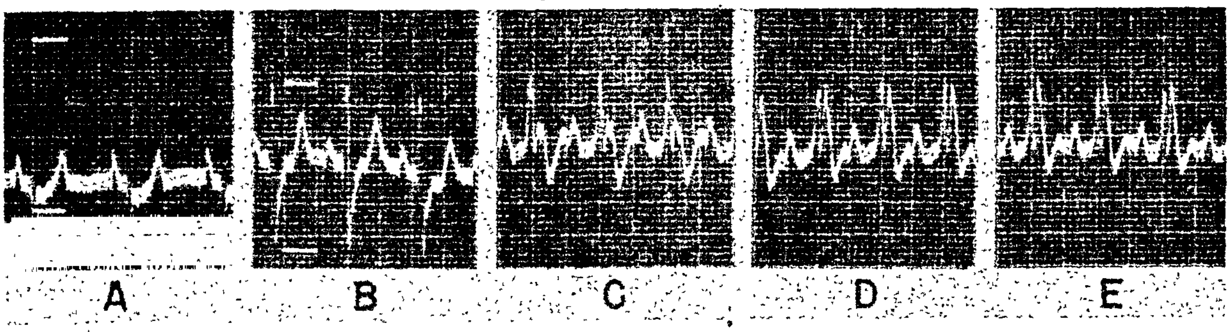

Fig. 1.—Effect of a rapid intravenous injection of procaine (300 mg. in fifteen seconds) on the P-R interval and QRS duration and contour (Lead II). The amplitude of QRS deflections is indicated by the short horizontal white markers in *A* and *B*. Note the development of first degree A-V block and of intraventricular block. Record *A* is the control. *B*, *C*, *D*, and *E* were taken at fifteen-second intervals after the injection.

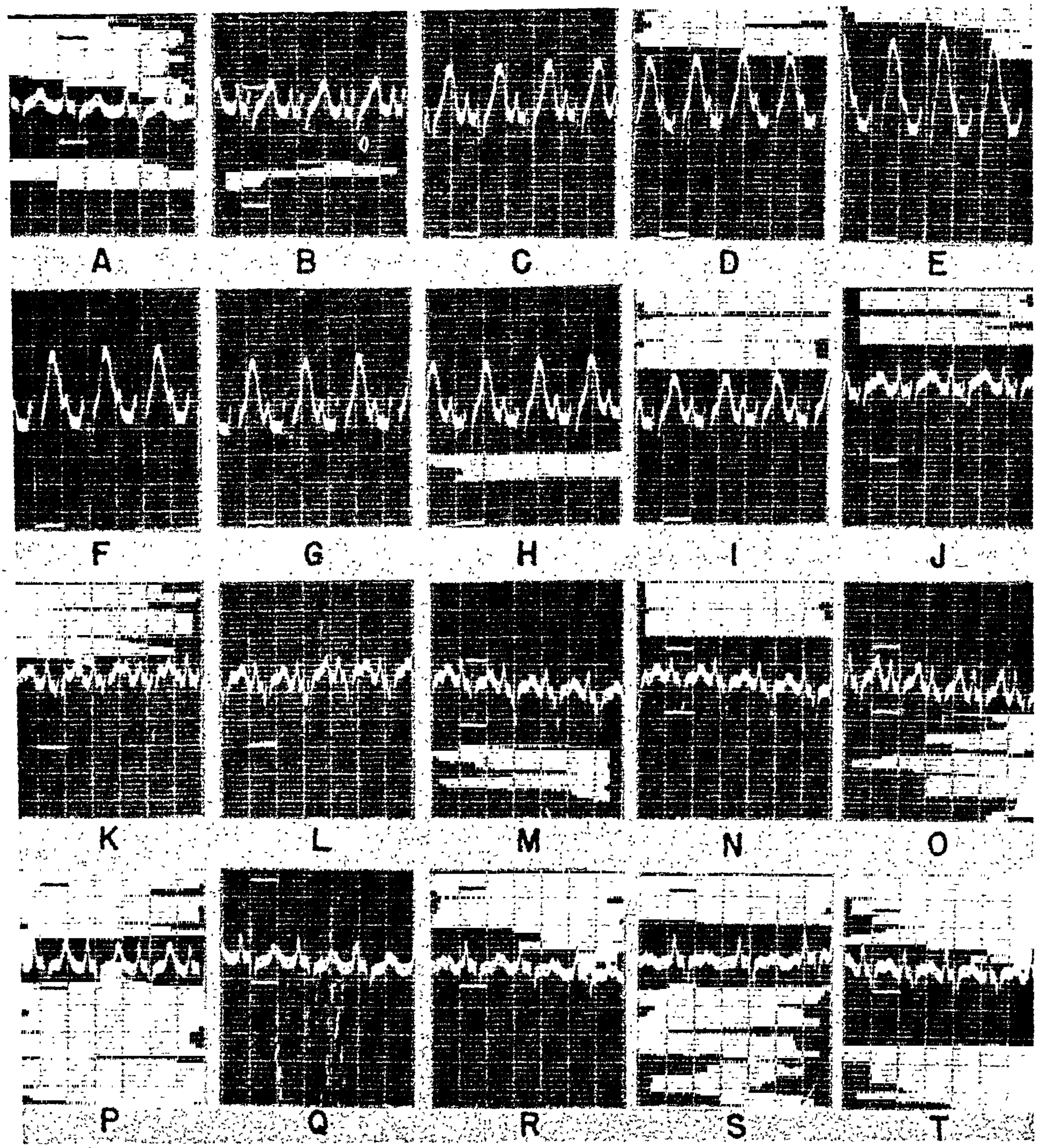

Fig. 2.—Progressive development of electrocardiographic changes (in Lead II) following injection of 50 mg. per kilogram of procaine intravenously in sixty seconds. Note increase in amplitude of P wave, prolongation of P-R interval, development of a deep S wave, and increase in duration of QRS; also, the early waxing and later waning of the T wave. *A* is the control. The time intervals following injection are as follows: *B*, fifteen seconds; *C*, thirty seconds; *D*, forty-five seconds; *E*, sixty seconds; *F*, one and one-half minutes; *G*, two and one-half minutes; *H*, three minutes; *I*, three and one-half minutes; *J*, six minutes; *K*, ten minutes; *L*, fifteen minutes; *M*, twenty minutes; *N*, twenty-five minutes; *O*, thirty minutes; *P*, thirty-five minutes; *Q*, forty minutes; *R*, forty-five minutes; *S*, fifty minutes; and *T*, fifty-five minutes. The horizontal white markers indicate amplitudes of the QRS complexes.

of injection; (2) an increase in the amplitude of the P wave; (3) a reduction in QRS amplitude in almost every instance, with the appearance of a deep S wave as the int aventricular block developed; (4) an increase in amplitude of the T wave independent of the change in heart rate.

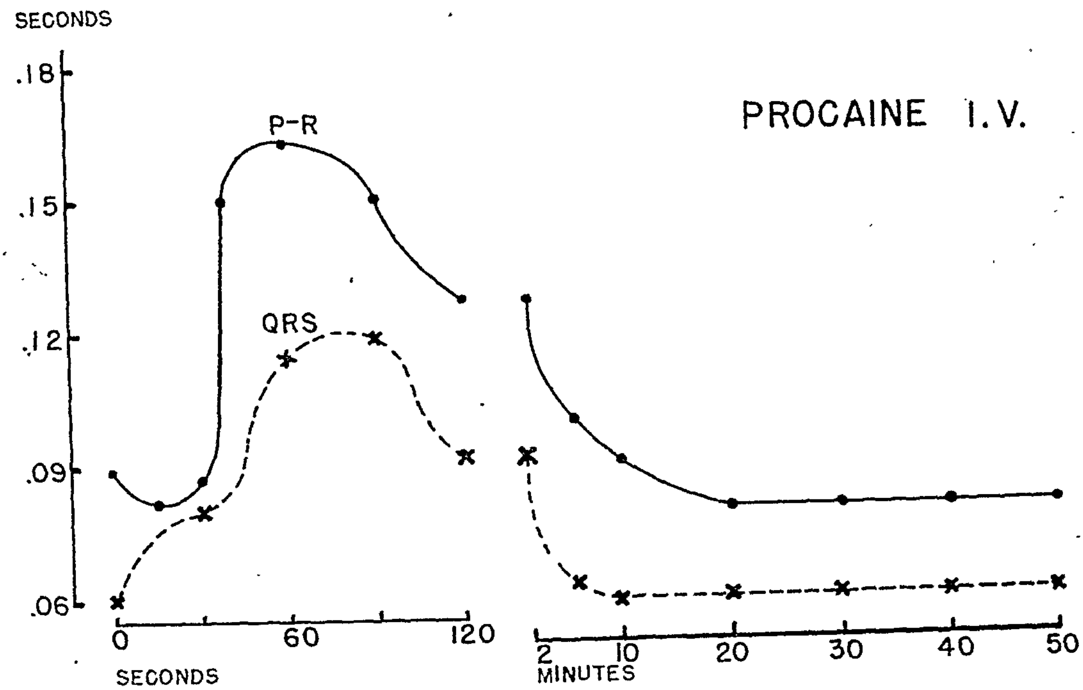

Fig. 3.—A graph illustrating the prolongation of P-R (solid line and dots) and QRS (broken line and crosses) following procaine injection. Time, abscissa; duration, ordinate. The values were obtained from the experiment shown in Fig. 2.

The progressive development of the electrocardiographic changes is illustrated in Fig. 2. Fig. 3 is a chart of the P-R and QRS changes which occurred in the preceding record. Fig. 4 shows the appearance of chaotic heart action following the very rapid injection of procaine intravenously.

DISCUSSION

From the observations noted it is apparent that procaine is a powerful depressant of the conduction system of the heart and progressively produces A-V and intraventricular block. It would appear, further, that there is an additional effect upon the myocardium, for the changes in QRS, S-T, and T configuration suggest some alteration in the depolarization and repolarization patterns.

Rapid administration of the drug intravenously is potentially capable of inducing a state of chaotic heart action as illustrated in one of the experiments. It is possible that this may have been the mechanism causing death in several of the clinical reports noted in the literature.

The changes in heart rate are probably the result of both cardiogenic and reflex factors. The slowing is most likely a reflection of the depressant action of the drug on the heart.

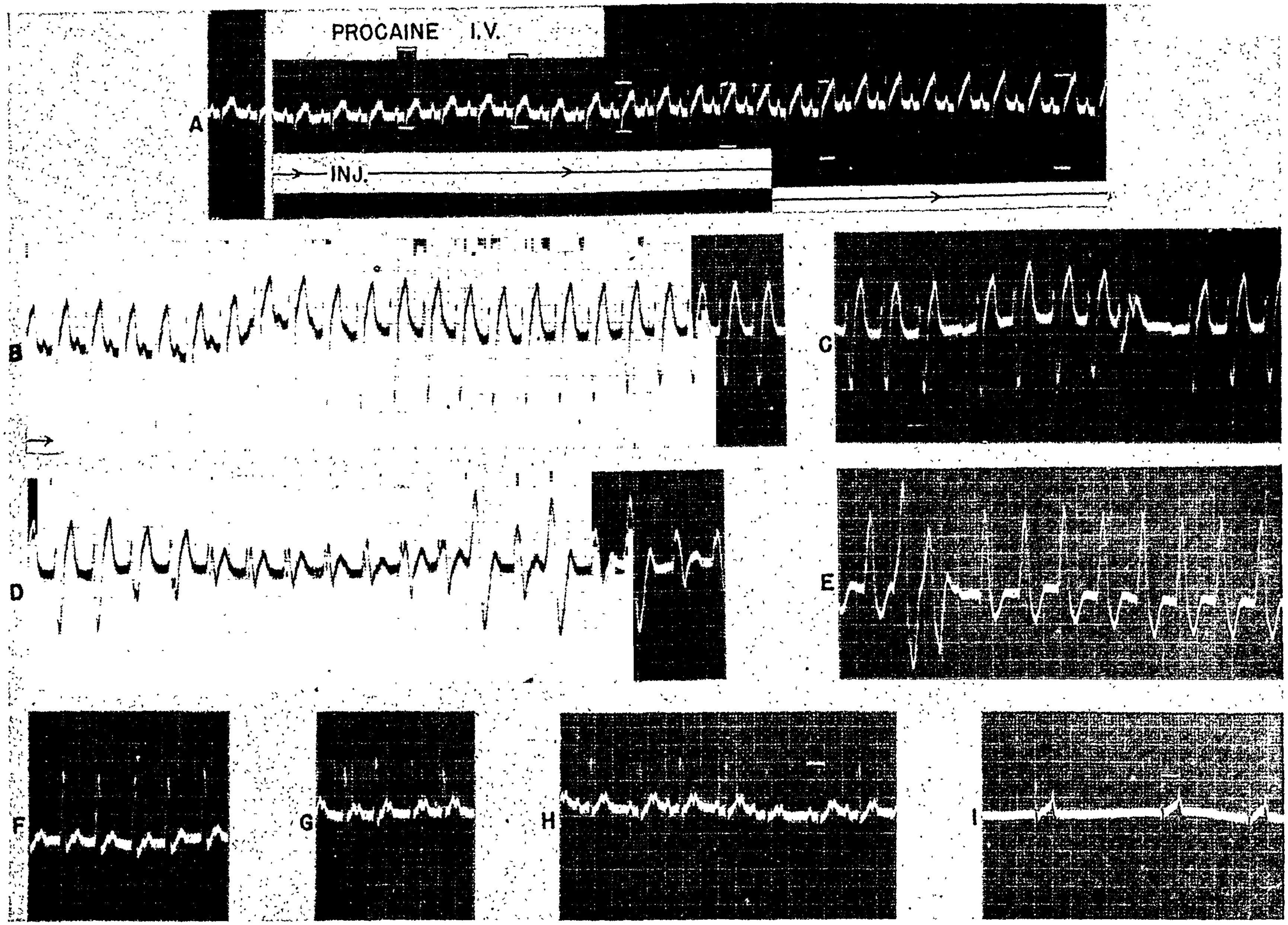

Fig. 4.—Chaotic heart action following the rapid injection of procaine intravenously (450 mg. in fifteen seconds); the period of injection is indicated by the horizontal arrow in *A* and *B*. *A*, control; *B* shows development of A-V and intraventricular block (note progressive merging of P wave with preceding T wave); *C*, *D*, and *E* show varying conduction disturbances in the ventricles and ectopic beats of ventricular origin (it is not possible to identify the P wave in these records); note notching of T waves in *F*, *G*, and *H*; P waves reappear in *H*; it is assumed that the tiny notch preceding the QRS complex in *I* is a P wave. The records were taken at the following intervals after injection: *B*, fifteen seconds; *C*, thirty seconds; *D*, one minute; *E*, two and one-half minutes; *F*, four minutes; *G*, five minutes; *H*, six and one-half minutes; and *I*, ten minutes. The horizontal white markers indicate amplitude of the QRS complexes.

It was felt that though the dosage level was high and the rate of administration rapid in these experiments, the potential hazards of the procaine could best be determined by evaluating the effects at their respective sublethal levels. Further, it should be borne in mind that hearts involved by inflammatory or degenerative lesions may tolerate only fractions of customary dosages of a given drug like procaine.

CONCLUSION

Intravenous administration of procaine in the pentobarbitalized dog caused significant changes in the electrocardiogram as evidenced by prolongation of the P-R and QRS intervals and by alteration of the configurations of P, QRS, S-T, and T deflections. In one instance it resulted in chaotic heart action with multiple ectopic pacemakers. Procaine is a powerful depressant of conduction.

We are indebted to Dr. L. N. Katz for his suggestions in the preparation of this report.

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HITHERTO UNDESCRIBED NEUROLOGICAL MANIFESTATIONS OF DIGITALIS TOXICITY

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THE involvement of the central nervous system in digitalis intoxication has been recognized and frequently reported in the literature since Withering's recognition of it in 1785.[1] Weiss[2] in 1932 stated that digitalis bodies acted directly on nervous structures, though the mechanism of action was not very well understood. Hueper and Ichniowski[3] and Dearing and associates[4] found extensive degenerative changes in the cortex, basal ganglia, cerebellum, pons, and spinal cord of animals made decidedly toxic with digitalis. These changes consisted of foci of vacuolated and disintegrating ganglion cells, necrosis, glial proliferation, and vascular changes.

The various neurological toxicities which have been reported are as follows: abnormal visual color sensations (especially yellow and green)[1,2]; blurred or dimmed vision[1,5-7,9-11]; diplopia[2,7,9,11]; temporary amblyopia[2,10,11]; scotomata[7-9,11]; flickering and glimmering of vision[2,10]; vertigo[2,5]; headache[2,5-7,10,11]; drowsiness[5,10]; malaise[10,11]; restlessness and irritability[2,5,9]; weakness and fatigue[2,5,6,8,11]; epileptiform convulsions[2,6,7,11]; hallucinations, illusions, and delusions[2,5,6,11]; confusion, disorientation, and delirium[2,7,9-11]; excitement or depression[2,5,7]; temporary loss of memory or aphasia[7,10,11]; and stupor and coma.[9] It should be noted that these toxic symptoms may occur regardless of the degree of toxicity and in the absence of any other manifestation of intoxication.

It is the purpose of this paper to present cases exhibiting peripheral and cranial nerve symptoms due to overdosage with digitalis products. These have not previously been reported, nor is there any reference in the literature wherein digitalis bodies are considered etiological factors in trigeminal or other neuralgias.

CASE REPORT

The following case was the first which drew our attention to these previously undescribed neurological aspects of digitalis toxicity.

M. V. was a 37-year-old white married woman with chronically active rheumatic heart disease involving both the mitral and aortic valves. She had presented the onset of diminished cardiac reserve at the age of 25 years. She had been digitalized several times for acute pulmonary edema, but the onset of rapid auricular fibrillation necessitated adjustment of digitalis dosage. The administration of a leaf product in doses of 0.2 Gm. three times daily for three days resulted

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in signs of toxicity manifested by anorexia, nausea, vomiting, and visual disturbances. Associated with these classical toxic symptoms was a severe facial pain characterized by a persistent aching of the teeth and lower jaw with superimposed lancinating pains along the distribution of the mandibular branch of the trigeminal nerve. Discontinuance of digitalis resulted in the cessation of all of these symptoms. Adjustment of digitalis dosage at repeated intervals over a three-year period was required for an uncontrolled rapid auricular fibrillation. On twelve separate occasions, similar attacks of facial pain associated with anorexia, nausea, vomiting, and green vision were noted. These symptoms occurred with the administration of digitalis leaf in doses of 0.1Gm. two or three times daily. Repeated dental examinations revealed no abnormalities.

This unusual case prompted us to review our experiences with toxic doses of various digitalis preparations to determine whether similar toxic manifestations were encountered. Studies in the evaluation of digitalis preparations and glycosides for the management of the ambulatory patient with congestive heart failure in progress for the past seven years lent themselves for this purpose. As part of this study, in order to determine the therapeutic range, the patient was given at periodic intervals an increasing dose of a digitalis preparation until minor signs and symptoms of toxicity supervened. The preparations studied included several lots of compressed tablets of Digitalis Purpurea, digitoxin, digoxin, lanatoside C, gitalin, urginin maritima, and urginin indica.

One hundred ninety episodes of toxicity were observed in ninety-six patients. Toxic episodes with different preparations in the same patient were counted as separate trials; but if more than one episode occurred with the same preparation, they were excluded. It is appreciated that patients may manifest the same toxic signs and symptoms to each of the preparations so that the incidence of any particular occurrence of an unusual symptom may be exaggerated. However, with a large group of subjects, the majority of whom had no more than two trials, this factor tends to be minimized.

Only the subjective manifestations of digitalis toxicity are considered here, since the true cardiac signs such as irregularities, arrhythmias, and various degrees of heart block may not have been present at the time the patient was examined in the clinic.

If each symptom is considered as a separate entity, a total of 600 occurrences of digitalis toxicity were observed in the 190 trials. These symptoms included anorexia, nausea, vomiting, diarrhea, abdominal pain, visual disturbances, weakness, nervousness, neuralgias and paresthesias, dizziness, headache, syncope, and tremors. It is of interest to note that approximately 41 per cent of the symptoms were neurological in nature. Neuralgias or related symptoms occurred thirteen times (2 per cent) in nine patients (9.4 per cent). The characteristics of these nine patients and the types of toxicity noted are presented in Table I.

DISCUSSION

The neurological manifestations of digitalis intoxication are more common than has been appreciated previously. Approximately 41 per cent of toxic symptoms involved some portion of the central or peripheral nervous systems.' Gastrointestinal complaints are only slightly more common but it is our belief that the incidence of their occurrence and the importance of their recognition as indications of digitalis toxicity have been overemphasized.

Table I

NUMBER	PATIENT	SEX	AGE	CARDIAC DIAGNOSIS*	DIGITALIS PREPARATION	DOSAGE RESULTING IN TOXICITY	TOXIC MANIFESTATIONS	REMARKS
1	J. W.	F	34	(1) Rheumatic fever—inactive (2) Enlarged heart, mitral stenosis, mitral insufficiency, aortic insufficiency (3) Regular sinus rhythm	Urginin indica	3.0 mg. daily for two weeks	Nausea, vomiting, dizziness, headache, toothache, tremors of fingers, nervousness	Associated diagnosis of idiopathic epilepsy well controlled with phenobarbital and dilantin; these symptoms subsided two days after stopping digitalis preparation
					Urginin indica	3.0 mg. daily for five weeks	Anorexia, nausea, vomiting, dizziness, headache, visual disturbances, weakness, toothache, shooting pains posterior aspect of thigh	All symptoms subsided two days after medication discontinued
					Gitalin	*1.25 mg. daily for six weeks*	*Nausea, vomiting, visual disturbances,* toothache, pain of jaw bilaterally, pain posterior aspect of thigh	*All symptoms subsided two days after* medication discontinued
2	J. S.	F	46	(1) Rheumatic fever—inactive (2) Enlarged heart, mitral stenosis, mitral insufficiency (3) Auricular fibrillation	Digitalis leaf	0.2 and 0.3 Gm. alternate days for two weeks	Blurring of vision, bilateral lower jaw aching, intermittent for two weeks	Decreased digitalis dosage resulted in subsidence of symptoms within forty-eight hours
3	M. B.	F	58	(1) Hyperthyroidism and unknown (2) Enlarged heart (3) Auricular fibrillation	Digoxin	0.75 mg. twice daily for one week	Anorexia, nausea, vomiting, headache, fatigue, tingling of fingers, nervousness	Decreased dose of digoxin resulted in subsidence of symptoms within three days
4	Z. P.	M	51	(1) Unknown (rheumatic type) (2) Enlarged heart, mitral stenosis, mitral insufficiency (3) Auricular fibrillation	Digitoxin	0.3 mg. daily for four weeks	Anorexia, nausea, headache, weakness, fatigue, generalized muscle pains	Associated diganosis of essential hypertension

5	L. S.	M	52	(1) Unknown (2) Enlarged heart (3) Auricular fibrillation	Urginin indica	1.5 mg. daily for nine weeks	Anorexia, nausea, vomiting, dizziness, blurring of vision, shooting pains, and weakness of both upper extremities	
6	J. M.	M	41	(1) Rheumatic fever—inactive (2) Enlarged heart, mitral stenosis, mitral insufficiency, aortic stenosis, aortic insufficiency (3) Auricular fibrillation	Digitoxin	0.4 mg. daily for two weeks	Anorexia, epigastric pain, dizziness, blurring of vision, nervousness, severe burning pain of feet	
7	R. F.	F	48	(1) Rheumatic fever—inactive (2) Enlarged heart, mitral stenosis, mitral insufficiency, aortic insufficiency (3) Auricular fibrillation	Digitalis leaf	0.2 Gm. daily for two weeks	Anorexia, nausea, mild bilateral facial pain, generalized myalgias	
					Urginin maritima	1.5 mg. daily for four weeks	Anorexia, nausea, dizziness, headache, blurred vision, weakness, toothache, and soreness of entire jaw	All symptoms subsided in five days upon discontinuation of therapy
					Gitalin	0.75 mg. daily for two weeks	Epigastric distress, blurring of vision, sensitivity of teeth, shooting pains bilaterally lower one-third of face	Associated dental caries
8	N. C.	F	75	(1) Arteriosclerosis (2) Enlarged heart, myocardial fibrosis, coronary sclerosis (3) Auricular fibrillation	Digitalis leaf	0.1 and 0.2 Gm. alternate days for three weeks	Anorexia, headache, blurring of vision, shooting pains of lower extremities, nervousness	Complete cessation of all symptoms upon discontinuance of digitalis leaf
9	M. C.	F	51	(1) Rheumatic fever—inactive (2) Enlarged heart, mitral stenosis, mitral insufficiency, aortic insufficiency (3) Auricular fibrillation	Digitalis leaf	0.25 Gm. daily for three weeks	Nausea, dizziness, diarrhea, blurring of vision, numbness of lips and tongue, toothache	Associated idiopathic thrombocytopenic purpura

*According to Nomenclature and Criteria for Diagnosis of Diseases of the Heart, New York Heart Association, 1939.

The ten patients presented exhibited unusual neurological complaints. A careful survey of the literature failed to disclose any previous recording of such symptoms. It is of interest to note that these complaints occurred in approximately 9 per cent of patients manifesting digitalis toxicity. Apparently the gastrointestinal symptoms have been considered to be the classical manifestations of toxicity, and their occurrence overshadowed any other subjective complaint. It has been our experience that neurological disturbances not only may occur earlier than the classical gastrointestinal symptoms, but also may be the only indication of digitalis toxicity.

The neuralgic type of pain usually involved the lower one-third of the face simulating the syndrome of trigeminal neuralgia. The pain was characterized usually as a dull aching in the teeth or as a sharp and stabbing pain throughout the mandible or maxilla, or both. Other areas involved with typically neuralgic "shooting pains" were the upper extremity, lower lumbar area with posterior thigh radiation, and calf muscles. Parasthesias, such as tingling in the fingers and burning sensations in the feet, were also observed.

The type of digitalis preparation administered apparently played no role in the occurrence of these neuralgic complaints. We noted this toxic manifestation with digitalis leaf, digitoxin, digoxin, gitalin, urginin maritima, and urginin indica. It is very probable that the other cardiac glycosides when used in toxic doses will produce the same type of toxicity.

SUMMARY

1. Ten patients with unusual neurological manifestations of digitalis toxicity are presented.

2. Neuralgic type of symptoms were noted in approximately 9 per cent of patients receiving a toxic dose of a digitalis preparation.

3. The high incidence of neurological manifestations of toxicity has not previously been appreciated.

4. Neurological symptoms may be the earliest, the most severe, and the sole manifestations of digitalis intoxication.

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ACUTE PERICARDITIS OF BENIGN TYPE

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IN CLINICAL practice, the finding of acute pericarditis is usually regarded as evidence of the presence of some serious underlying disease such as rheumatic fever, myocardial infarction, uremia, tuberculosis, or pneumonia. There are, however, cases of pericarditis which pursue a relatively benign clinical course without evidence of any other disease. Recognition of these cases is highly desirable since their differentiation from other types of pericarditis and myocardial infarction is of great importance. Several descriptions of this benign form of pericarditis have appeared within recent years.[1,4,19] It is our impression that this condition is still not well known and that cases are being overlooked. The purpose of the present article is to describe seventeen additional examples of this condition, and particularly, to discuss the electrocardiographic findings which are of great value in the differential diagnosis (Table I).

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Based upon observations of our own cases and upon previous reports in the literature, the following is a general description of acute "non-specific" (idiopathic) pericarditis. Chest pain is the outstanding symptom. This most frequently occurs in the substernal or epigastric region but may be located also in the anterior chest, to either side of the midline, or in the shoulder. The pain may be quite severe, but is usually not as intense as that of myocardial infarction. It is commonly sharp and is characteristically aggravated by deep inspiration, turning of the body, coughing, sneezing, and, rarely, by swallowing. The discomfort may extend across the whole of the front of the chest, or may remain localized to the precordium. Radiation to the angle of the left scapula, to the neck, suprascapular region, or even down one or both arms may occur. The pain may be lancinating and intermittent, in contrast to that of myocardial infarction which is usually not sharp, and which is more often constantly present from inception until its gradual subsidence. Patients have variously described the discomfort as "sharp and cutting," "crushing," "pressing," or as a "feeling of indigestion." The duration is usually one to two days, but at times it recurs later during the course of the illness. Occasional twinges of pain may be experienced for some months. In rare instances, pain is insignificant.

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TABLE I. THE CLINICAL AND ELECTROCARDIOGRAPHIC FEATURES PRESENT IN SEVENTEEN CASES OF ACUTE PERICARDITIS OF BENIGN TYPE

CASE	AGE	ANTECEDENT RESP. INFECTION	FRICTION RUB	MAXIMUM WBC	MAXIMUM SED. RATE	MAXIMUM TEMP.	DURATION OF FEVER (DAYS)	PAIN	SIGNIFICANT ELECTROCARDIOGRAPHIC FINDINGS
1	40	0	+	10,000	20	101°F.	2	Severe precordial pain	S-T elevation I, II, III, and IV; T-wave inversion I, II, and IV
2	22	+	0	12,400	30	103°F.	3	Crushing substernal pain	S-T elevation I, II, III, and IV; T waves of increased amplitude; T-wave inversion I, II, III, and IV
3	46	+	+	10,000	0.8 to 1.2 mm. 48 to 72	100.8°F.	4	Pain in left shoulder aggravated by deep breathing, sneezing, and change of position; precordial tightness radiating to neck	S-T elevation II, III, and CR_4; T-wave inversion in I, II, III, and IV
4	25	+	0	10,200	—	100°F.	1	Griping, in epigastrium; shocking, stifling feeling	S-T elevation I, II, and CF_4; T-wave inversion in I, II, and III
5	22	0	+	11,200	—	101°F.	4	Sharp precordial pain	S-T elevation I and II; T-wave inversion in I, II, III, and IV
6	25	+	0	16,400	—	102.8°F.	5	Precordial ache radiating to left arm; feeling of indigestion	S-T elevation I, II, and IV; T-wave inversion in I, II, III, and IV
7	29	+	0	12,000	—	—	—	Muscular soreness followed by intermittent sharp precordial pain	S-T elevation I and II; T-wave inversion in I
8	32	0	+	12,000	42	101°F.	4	Severe indigestion; intermittent squeezing substernal pain	S-T elevation I and II; T-wave inversion in I, II, III, and CF_2

9	25	+	+	13,660	37	99.6°F.	1	Substernal pain and tightness radiating to left arm	S-T elevation I and II; T-wave isoelectric in I
10	18	+	0*	15,000	60	104°F.	7	Sudden severe precordial pain	ECG not taken at onset; T-wave inversion in I, II, III, and IV
11	39	—	0	8,000	16	100°F.	2	Excruciating precordial "scratching feeling"	S-T elevation I and IV; T-wave inversion in I, II, and III
12	34	0	0*	9,200	—	—	—	Sharp precordial pain	S-T elevation II and III; isoelectric T_1, diphasic T_2 and T_3
13	24	+	+	9,500	—	100.4°F.	3	Sharp substernal pain radiating to left shoulder	S-T elevation I and II
14	25	+	+*	13,900	72	102.8°F.	6	Precordial cramp with radiation to neck and left arm	S-T elevation I and II; T-wave inversion I, II, and IV
15	25	0	+	8,500	48	100.2°F.	3	Sharp precordial pain aggravated by inspiration, coughing, and turning	S-T elevation I, II, and III; T-wave inversion I, II, and IV
16	20	+	0	Normal	34			Intermittent pain over left upper chest	T-wave inversion in I, II, III, and IV
17	26	+	0	Normal	29	100°F.	2	Dull precordial pain and numbness of left arm	S-T elevation II and III; T-wave inversion I, II, and III; notched T in CF_4
3 (Second admission)	46	+	0		66	100°F.	3	Aching beneath left shoulder	T-wave inversion I and IV

*Pericardial effusion.

Dyspnea may be present as a result of the splinting of the chest. Syncope at the onset of pain or a drop in blood pressure to shock levels may occur, but such occurrence is rare.

A pericardial friction rub is frequently present, although not always detected. Repeated examination with the patient leaning forward in forced expiration, as well as in the recumbent and lateral positions, may be necessary for its demonstration. The rub usually disappears within twelve to twenty-four hours. Pericardial effusion occurs in some instances, and some observers feel that the heart may undergo actual dilatation.[1,2] The frequency of pericardial effusion is emphasized by a recent report of eight cases from a United States Army hospital[3] which may have been instances of this type of infection.

Fever usually occurs at the time of onset of pain and is usually mild, varying from 101° to 102°F. and lasting only a few days. It may reach 104°F. and persist as long as one week. Profuse perspiration is not uncommon. Most of the patients feel remarkably well after the first few days. Following recovery, there are no symptoms to suggest angina pectoris and none of the stigmata of rheumatic fever or rheumatic heart disease are present.

Recurrence of pericarditis is occasionally observed, and some authors[1] have suggested that this type of infection may at times be a factor in the etiology of constrictive pericarditis. Other serous membranes may be involved, and a history of previous pleurisy or the presence of an associated pleurisy is not infrequent.[4] Cases have been noted postoperatively, apparently unrelated to respiratory infection or pulmonary embolism.

Leucocytosis of a mild degree is common, although the leucocyte count is at times normal. The sedimentation rate is almost invariably elevated, but returns to normal in one to two weeks.

There is no specific treatment. The disease is self-limited, and the clinical features are frequently so brief that it would be most difficult to evaluate therapy. Sulfonamides and penicillin have had no apparent effect on the course of the disease.

ELECTROCARDIOGRAPHIC FINDINGS

The manifestations of pericarditis in the electrocardiogram have been demonstrated to be due to subepicardial myocarditis.[5-8] In the acute stage, the S-T segments become elevated in one or more leads. The elevation may occur in all leads or may be confined to Leads I and II, or Leads II and III, with or without elevation of the S-T segments in the precordial leads (Fig. 1). In rare instances, the S-T elevation may be confined to Lead I. The elevation may vary from 0.5 to 2.0 millimeters. In order to evaluate small amounts of elevation, it is necessary to have serial tracings, since it is not uncommon to find an elevation of 0.5 to 1.0 mm. in the tracings of normal individuals.[9,10] The S-T segments are concave, in contrast to the convex or cove plane segments so often seen in myocardial infarction. After one or two days, the S-T segments become horizontal or rectilinear, though still elevated, and the T waves become lower in amplitude (Fig. 2). There are never the reciprocal changes of the S-T segments such as occur in myocardial infarction. In pericarditis, if S-T changes are present, they are always in the

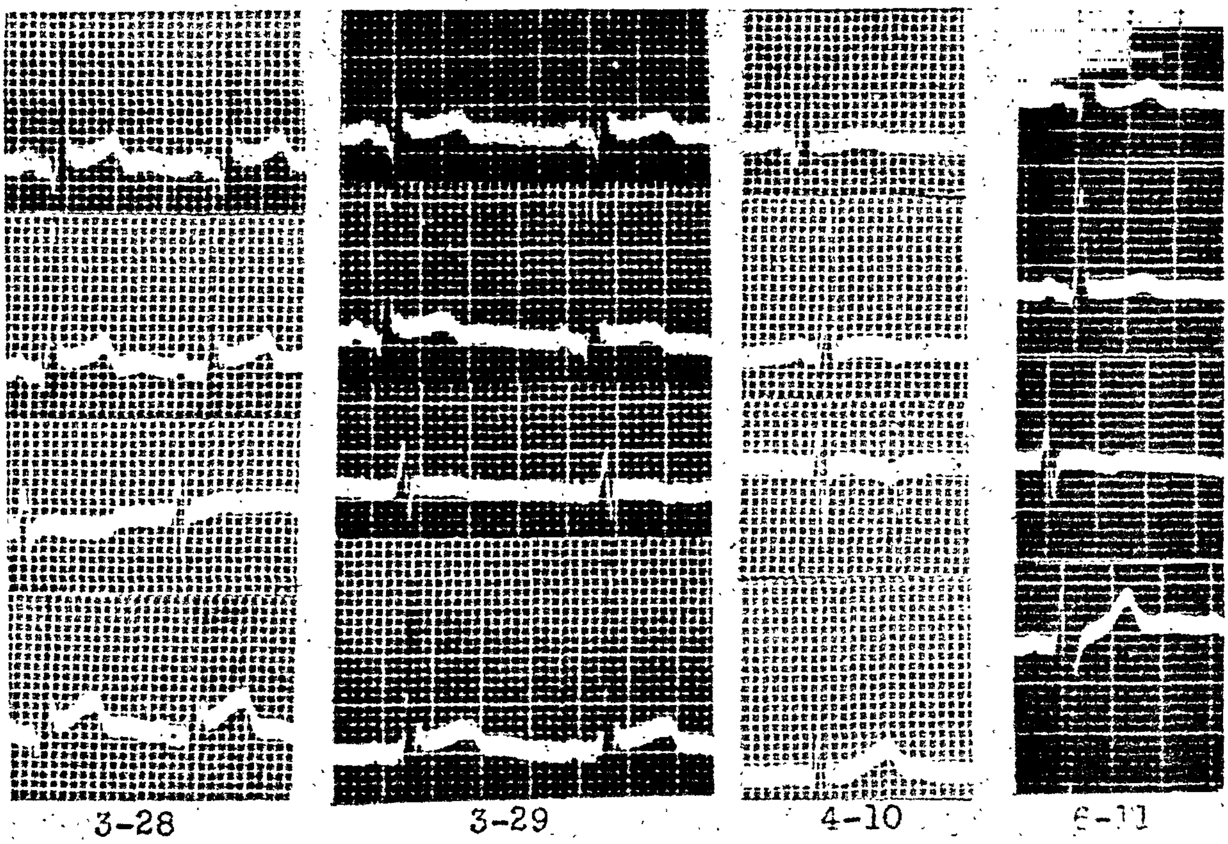

Fig. 1.—Case 7. The S-T segments are elevated on March 28. On April 10 T_1 and T_2 are beginning to invert. Note that there is no change in the normal Q_1 through the series of tracings. There is no reciprocal depression of $S-T_3$ as might be expected if this were myocardial infarction.

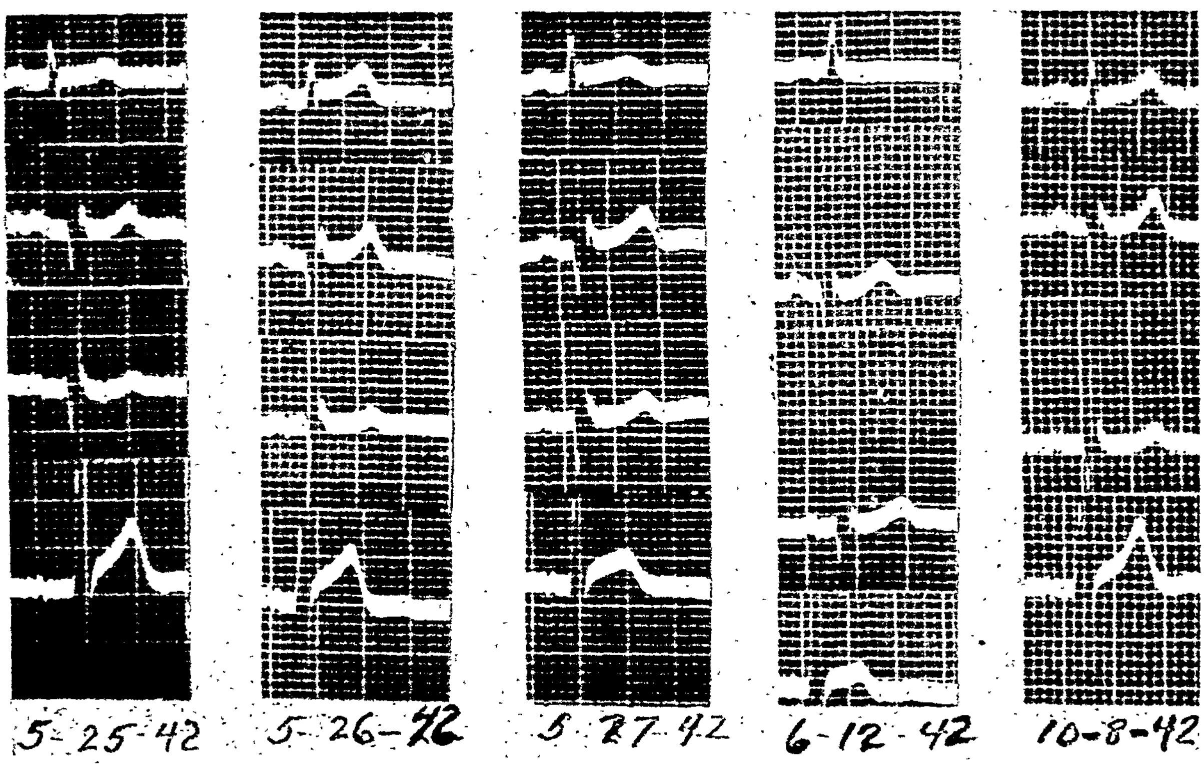

Fig. 2.—Case 3. On May 26 the S-T segments are elevated in Leads I, II, III, and CF_4. The T waves in Leads I and CF_4 are slightly inverted on May 27. Tracing is normal on October 8. Note that the Q waves in Leads II and III did not change throughout the series of tracings; these represent a normal variation for this individual.

same direction. Ordinarily, the QRS complexes are not affected, but in the presence of pericardial effusion, their amplitude may be lowered. Q waves do not occur as a result of pericarditis, in contrast to their presence in myocardial infarction. Q waves at times may be observed as a normal variation of an individual's tracing, but in these instances they do not change when serial tracings are taken. Auricular-ventricular conduction time remains normal, an important consideration in the differentiation from rheumatic fever.

The T waves may be abnormally tall and sharply pointed at onset, particularly in the precordial leads, but they soon become lower in amplitude and flattened. Usually after about a week they begin to invert and remain inverted from a few days to several months (Fig 3). Inversion occurs in one or more leads;

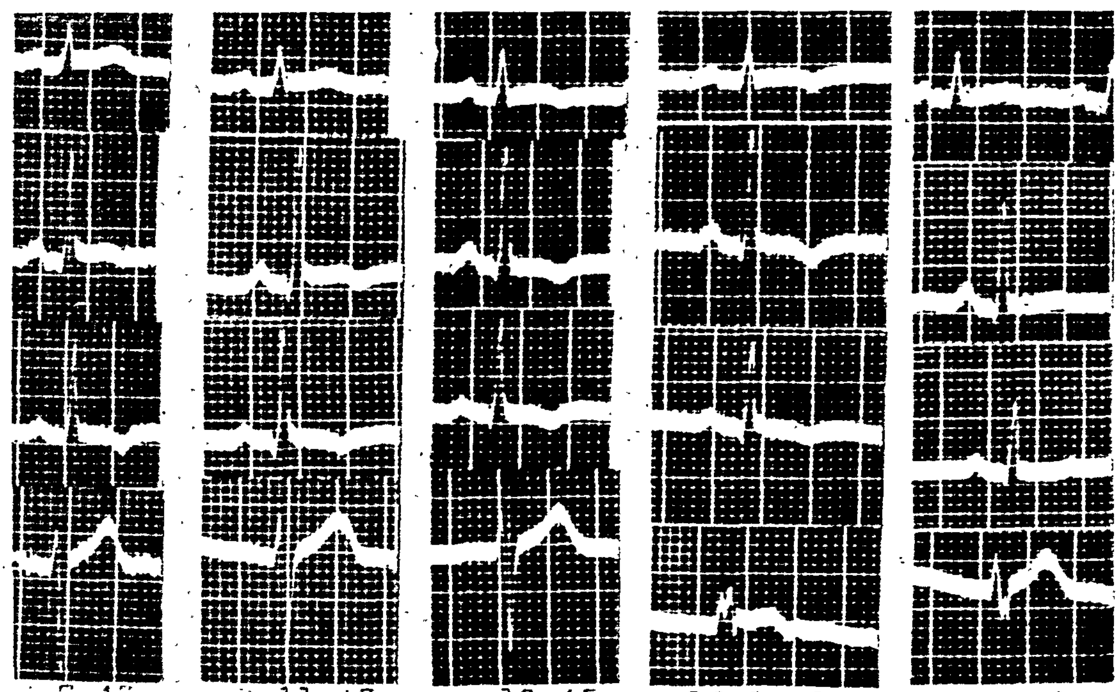

Fig. 3.—Case 6. The S-T segments are elevated in I, II, and III with inversion of T_2 and T_3 on September 7. On September 18 the T waves are inverted in I, II, and III. The precordial lead taken on October 1 was CF_2. This shows an M-shaped QRS and a QRS interval of 0.08 second. The single precordial lead of November 2 was apparently taken at the transitional zone. Tracing of November 2 shows residual flattening of the T waves in the standard leads.

at one time or another, the T waves may be inverted in all leads. Unless repeated tracings are taken, the stage of T-wave inversion may be missed. The changes in the T waves may fluctuate from day to day; one day the tracing may be abnormal, the next it may be normal, and on still another day, may again be abnormal. It has been suggested that this fluctuation is related to variations in the amount of edema or inflammation of the myocardium. This seems unlikely, and certainly the clinical manifestations do not parallel the electrocardiographic changes. It may be related to neurogenic influences.[2,8] The T-wave changes can be altered by the use of autonomic drugs, but the T waves do not completely

return to normal in individuals with vasomotor instability.[11] Generally, the electrocardiogram returns to normal after about four to eight weeks, leaving few or no residual changes.

CASE REPORTS

The following case reports are representative of the group.

CASE 2.—A 25-year-old soldier had been subject to repeated sore throat. He was hospitalized May 25, 1943, with acute tonsillitis and was returned to duty one week later. He continued to experience bouts of sore throat and on July 9 developed a feeling of indigestion and heaviness in the left upper abdomen with a sense of aching over the precordium. He felt as if belching would bring relief. The pain was aggravated by deep breathing and radiated to the left arm. There was some dyspnea. The temperature was 100.2° Fahrenheit. Nine days later there was a recurrence of sore throat with fever of 103° and recurrence of precordial pain. No friction rub was heard. The leucocyte count was 16,400. He was transferred to a general hospital with a diagnsois of anterior myocardial infarction. The initial tracing taken July 9, 1943, showed elevation of the S-T segments in Leads I, II, III, and CF_4 (Fig. 4). On July 10, 1943, there was late inversion of the T waves in Leads I, II, and CF_4. Two days later, on July 12, 1943, the tracing had returned to normal. A tracing on July 22, 1943, showed deep inversion of the T waves in Leads I, II, III, and CF_4. A tracing on Aug. 26, 1943, showed slight inversion of the T waves in Leads I and CF_4. The electrocardiogram was normal on Nov. 13, 1943. There were never any reciprocal changes, no Q waves, and no change in the auriculoventricular conduction time.

Comment.—The rapid fluctuation of the pattern is worthy of comment, particularly the return to normal two days after deep inversion of the T waves had been present. In our experience this is not uncommon in acute pericarditis. The patient developed a severe cardiac neurosis and he was subsequently discharged from the service.

CASE 4.—A 22-year-old soldier suddenly developed sore throat, generalized body aching, and fever on the day prior to his hospitalization. The following day he experienced a sudden severe, crushing substernal pain which radiated straight through to the back and seemed to limit his breathing. It was aggravated by deep inspiration and movements of the trunk. There was no history of antecedent rheumatic fever and no joint pains with the current illness.

At the time of admission to the hospital, his temperature was 103.4°F.; it subsequently became normal, except for a spike to 101° several days later. The heart, clinically, was normal. No pericardial friction rub was heard.

The leucocyte count was 12,400. The sedimentation rate was 30 mm. in one hour (Wintrobe). An electrocardiogram taken Feb. 5, 1943, showed elevation of the S-T segments in all leads (Fig. 5). The T waves were of increased amplitude, measuring 9.0 mm. in Lead II and 12 mm. in Lead CF_4; however, the tracing was overstandardized 2 millimeters. A tracing taken Feb. 6, 1943, revealed that the T waves were of lower amplitude and that the S-T segments were rectilinear in Leads I, II, and CF_4, being isoelectric in Lead III. On Feb. 24, 1943, the S-T segments had returned to the isoelectric level, and there was beginning inversion of the T waves in all leads, with slight lowering of the amplitude of the QRS complexes. A tracing on March 10, 1943, was entirely normal. The conduction time was never more than 0.20 second.

Comment.—Pericarditis in this instance was also related to an acute upper respiratory infection. The unusual feature of the case was the marked increase in amplitude of the T waves in all leads at the onset of the illness. In all other respects, the evolution of the electrocardiographic pattern conformed to the

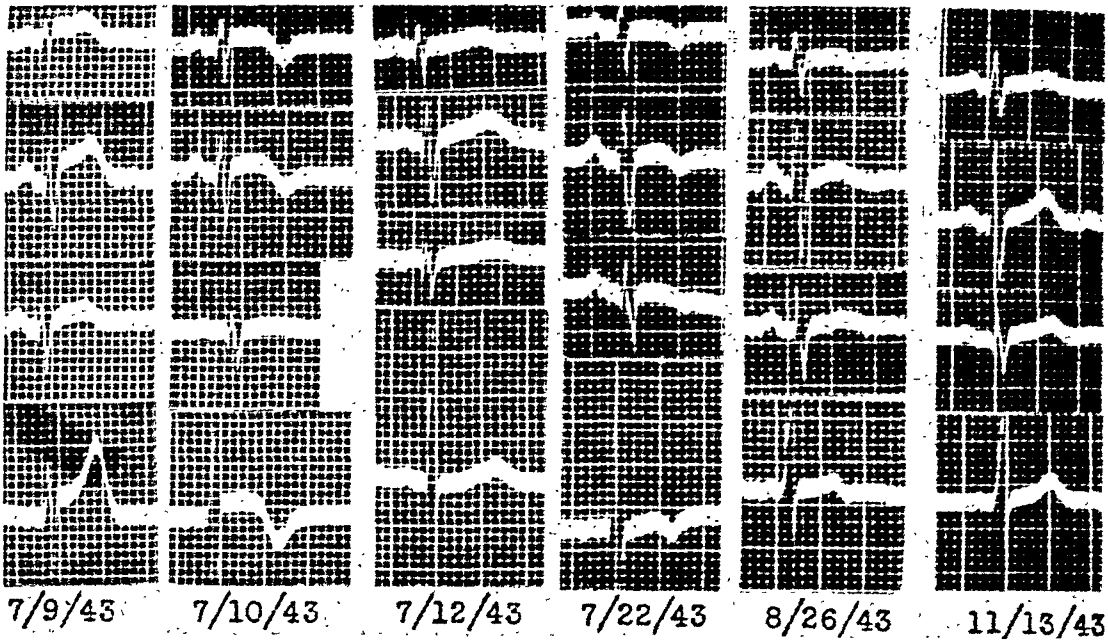

Fig. 4.—Case 2. The S-T segments are slightly elevated in all leads with beginning inversion of T_1 on July 9. A striking change has occurred on July 10 with deep inversion of T in I, II, and CF_4. Two days later the tracing has reverted to nearly normal. On July 22, the T waves are inverted in all leads, and on November 13, the tracing has returned to normal.

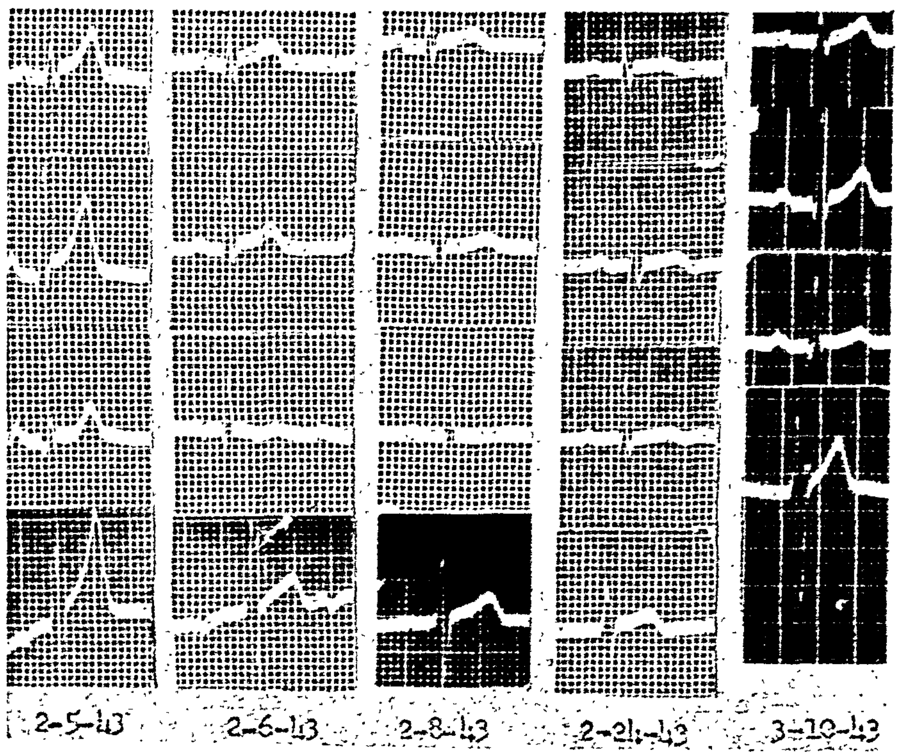

Fig. 5.—Case 4. The S-T segments are elevated in all leads on February 5. On February 24 the T waves are slightly inverted in all leads. The tracing of March 10 is normal.

criteria established for acute pericarditis. The S-T segments were elevated in all the leads in the initial record, and later the T waves showed beginning inversion in all leads. The tracing returned to normal in about one month.

CASE 5.—A 40-year-old soldier developed sudden severe precordial pain and syncope following an exhausting train trip. The pain was aggravated by deep inspiration and radiated to the left side of the neck. Turning in bed caused an increase in the discomfort. He was admitted to the hospital with a tentative diagnosis of coronary occlusion. There was a fever of 101°F. for two days, and a pericardial friction rub was heard during the second twenty-four hours. The leucocyte count was 10,000, and the sedimentation rate was 20 mm. in one hour (Wintrobe). One week later the sedimentation rate was normal. A tuberculin test using 0.01 mg. of purified protein derivative was negative. The pain subsided after twenty-four hours, and convalescence was uneventful.

An electrocardiogram made at the time of admission revealed an elevation of the S-T segments in all leads (Fig. 6). A tracing taken the next day showed progressive changes with some lowering of the amplitude of the T waves. A tracing taken April 2, 1944, showed beginning inversion of the T waves in Lead II with a horizontal S-T segment in Lead III. On April 6, 1944, the T waves were inverted in Leads I and IV and were flattened and slightly notched in Lead II. The S-T segments had become isoelectric in Leads I and III. On the following day, the T waves were inverted in Leads I and IV and were upright in Lead II, the S-T segments having returned almost to normal. An electrocardiogram taken May 3, 1944, was normal.

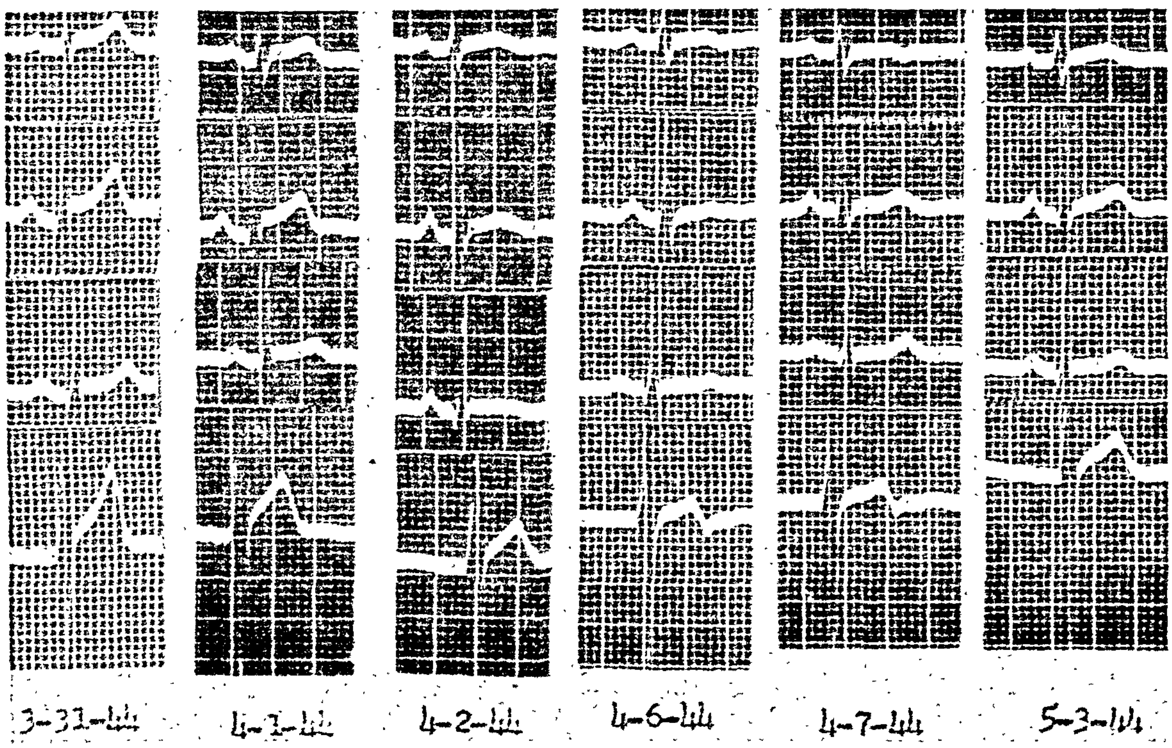

Fig. 6.—Case 5. The S-T segments are elevated in all leads on March 31. On April 6 the T waves are inverted in I and CF_4 with diphasic T_2, and the S-T segments have returned to the isoelectric line. Tracing of May 3 is normal.

Comment.—In this instance there was no history of associated respiratory infection. The associated syncope is an unusual manifestation of pericarditis. The admission diagnosis was coronary occlusion, but the evolution of the electrocardiographic pattern in serial records permitted the correct diagnosis of acute pericarditis to be made.

CASE 15.—A 46-year-old officer was admitted to the hospital March 1, 1945, complaining of pain in the left shoulder and a sense of pressure in the anterior chest which radiated to the neck. The patient had previously had an upper respiratory infection for about one month with an increase in severity of symptoms during the preceding week. Three days prior to admission he developed a nagging pain in the left shoulder, aggravated by deep breathing, change in position, coughing, and sneezing. On the next morning, there was a tightness across the front of the chest which extended into the neck. Subsequently, there was epigastric pressure which seemed to extend down from the chest. It was necessary for him to spend the night sitting up. He was feverish, had a "grippy feeling," and his teeth seemed to ache. There was no antecedent history of rheumatic fever. In 1943 he had had a similar episode of chest pain, following an upper respiratory infection, which had lasted two days. He had not been hospitalized at that time, and one electrocardiogram had been presumably normal.

The blood pressure was 110/60. The cardiac rhythm was regular, with a rate of 108 per minute. The patient appeared uncomfortable and protected the left shoulder from movement. The heart was of normal size and the sounds were of good quality. A faint, scratchy pericardial rub was heard at the third left intercostal space. There was slight tenderness over the left deltoid region. The leucocyte count was 10,450 with 71 per cent neutrophiles and 29 per cent lymphocytes. The urine was normal. The initial sedimentation rate was 1.2 mm. per minute by the Rourke-Ernstene method, gradually returning to normal during the next three weeks. A blood culture showed no growth. The Kahn test was negative. An x-ray film of the chest showed obliteration of the left costophrenic angle, with slight thickening of the pleura over apices of both lungs. An electrocardiogram taken March 1, 1945, three days after onset, revealed elevation of the S-T segments in Leads II, III, and CF_4 (Fig. 7). On March 3, 1945, the T waves had become flattened in Leads I, II, and III and slightly inverted in Leads CF_4 and CR_4. The S-T segments were still elevated in Leads II and III, but were horizontal. On March 4, 1945, the T waves were inverted in Leads I, II, CF_4, and CR_4. On March 20, 1945, the T waves had become upright in CF_4. The tracing was within normal limits on June 26, 1945, except for a slight degree of right axis deviation which had been constant throughout the series of tracings. In September, 1945, the patient was readmitted to the hospital with another similar attack accompanied by transient elevation of the sedimentation rate and the serial electrocardiographic changes of acute pericarditis. He experienced one further episode in November, 1945, and was subsequently transferred to a general hospital for disposition.

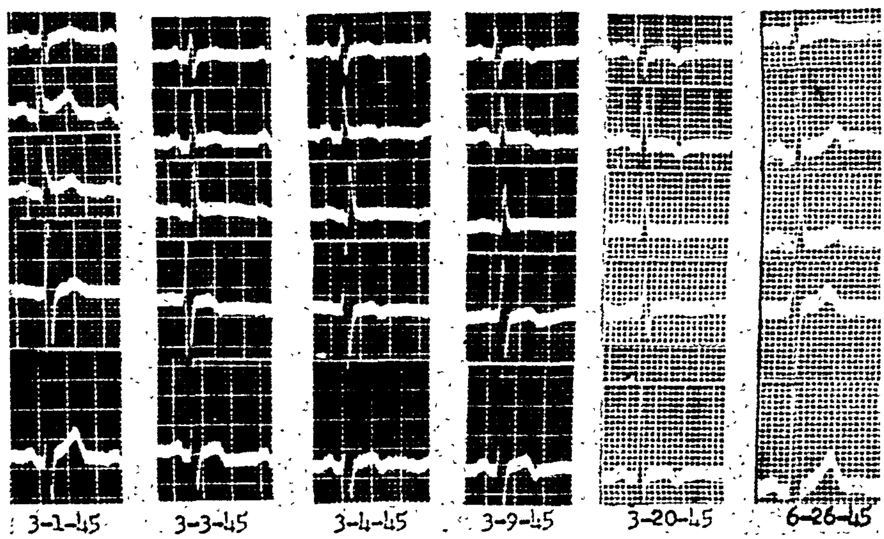

Fig. 7.—Case 15. On March 1, the S-T segments are elevated in II and III. On March 20, the T waves are inverted in Leads I, II, III, and CF_4 and are flattened in CF_2. The tracing of June 26 is normal, except for an unimportant degree of right axis deviation which is present throughout the series of tracings.

DISCUSSION

During the same period in which these cases were observed, one of us (R. B. L.) observed a total of forty cases of pericarditis the etiology of which was as follows: "Non-specific," 15; rheumatic, 15; tuberculous, 4; neoplastic, 3; traumatic, 1; rheumatoid arthritis, 1; and acute disseminated lupus erythematosus, 1. There were, in addition, twenty-four cases of acute myocardial infarction in the age group from 20 to 40 years, and we were alert to the occurrence of this disease in young soldiers. The frequency of the "non-specific" type emphasizes its importance. It is probable that it is often overlooked in civilian life where the use of the electrocardiograph remains more limited.

The etiology of benign pericarditis is unknown. It is frequently, however, a sequel to upper respiratory infections.[17,18] This is probably the same type of pericarditis which has been reported as a complication of atypical pneumonia.[2,3,12,15] It may, perhaps, be the pericardial counterpart of the common variety of pleurisy associated with upper respiratory infections. Hargrove[16] reported a case of acute pericarditis due to *Streptococcus viridans*. Antistreptolysin titers were determined in two patients in the present series by Dr. Charles Rammelkamp.[20] These were normal, suggesting that hemolytic streptococcal infection and rheumatic fever were not responsible for the pericarditis. Dr. Rammelkamp studied two additional cases of acute "benign" pericarditis, and in each instance the antistreptolysin titers were normal. The possibility that this may represent an antigen-antibody reaction with sensitization of the pericardium and subsequent inflammatory reaction on exposure to bacterial antigen cannot be excluded. Three patients in this series gave a history of previous attacks, and one (Case 15) had a total of four attacks. This susceptibility to reinfection is similar to that seen in rheumatic fever.

That cases of acute pericarditis are still being confused with coronary disease is demonstrated by reports in the literature. Weinstein[13] reported ten cases of "atypical" coronary disease in young soldiers, and it seems probable that some of these were actually cases of pericarditis. Certainly Cases 2 and 5 of his series showed serial electrocardiographic changes of pericarditis. Case 2 was probably an instance of "benign" pericarditis, but Case 5 was probably one of rheumatic pericarditis. In the latter patient, there was an associated polyarthritis, and the antistreptolysin titer rose to 833 units. Clagett[14] reported a case of probable coronary disease with occlusion following fever therapy. A review of this case shows that the clinical and electrocardiographic findings were those of acute pericarditis, probably of the benign type. In discussing this patient he stated that the sudden change in the electrocardiogram during the second week of the illness, when the tracing returned toward normal and then on the next day suddenly reverted to an abnormal configuration, was more indicative of coronary thrombosis. In our experience, this is suggestive of pericarditis rather than myocardial infarction in which the changes remain relatively fixed once the pattern is established.

The importance of differentiation of pericarditis from myocardial infarction is obvious. The fact that a pericardial friction rub is not heard does not rule out the former; only eight of seventeen cases of pericarditis showed such a rub.

The frequency of the detection of a rub will depend upon how carefully and how frequently the patient is examined. The rub may be transient just as in myocardial infarction. Unless tracings are obtained early during the stage of S-T segment changes, it may be difficult to evaluate and differentiate the changes from those of a small myocardial infarct. The average age of patients with "benign" pericarditis is generally lower than that of patients with myocardial infarction. However, the increasing frequency with which myocardial infarction is recognized in young persons only serves to make the problem more difficult. Six of seventeen patients in the present series were considered as cases of probable coronary occlusion at the time of hospitalization, and the evolution of the electrocardiographic changes allowed the establishment of the proper diagnosis of pericarditis. Although none of the patients came to necropsy, the symptoms, course, and electrocardiographic changes gave strong evidence of pericarditis.

SUMMARY

1. Seventeen cases of acute pericarditis of benign type observed in the military service are reported.

2. Pain was the outstanding complaint, and in six instances a diagnosis of myocardial infarction had been made or had been entertained initially.

3. Serial antistreptolysin titers were determined on the serum of two patients and were found to be normal.

4. A tendency for recurrence of the disease was noted; three patients had more than one attack.

5. Rapid fluctuations of the changes in the electrocardiogram were at times noted.

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ACUTE MYOCARDIAL INFARCTION: DETAILED STUDY OF DICUMAROL THERAPY IN SEVENTY-FIVE CONSECUTIVE CASES

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THE addition of Dicumarol to the therapeutic armamentarium for the management of acute myocardial infarction increases the probability of significantly reducing the deaths and vascular complications accompanying the acute infarction. Although fatalities from acute myocardial infarction have been reduced through more rapid, accurate diagnosis and improved treatment, the mortality is still great enough to stimulate investigation of additional therapeutic agents. Dicumarol has been administered with excellent results as a prophylaxis for peripheral thromboembolic disease since 1942.[1] The most recent extension of the use of this anticoagulant has been in the management of acute myocardial infarction, a disease in which thromboembolic lesions are an important factor in the high mortality rate.

Prevalence of Thromboembolic Complications in Acute Myocardial Infarction.—There are numerous references in the medical literature which emphasize the importance of the tendency toward intravascular clotting as a complication after myocardial infarction. In a post-mortem study of 160 cases of acute coronary occlusion, Hellerstein and Martin[2] found that thromboembolic lesions were the chief cause of death in 15 per cent of the cases, and a contributory cause in an additional 12 per cent. Garvin[3] found mural thrombi present in the hearts of 67 per cent of patients dying of acute myocardial infarction. In reviewing the literature, Hellerstein and Martin[2] report that of 577 patients dying after an acute myocardial infarction, 10 per cent died of pulmonary embolism. Clinical evidence of thromboembolic disease accompanying the occlusive coronary episode has been reported by numerous investigators. Master and associates[4] observed 500 patients with acute myocardial infarction. They reported a 6 per cent mortality due to clinical embolism. Woods and Barnes[5] found massive pulmonary embolism to be the cause of death in six of their sixty patients with acute coronary occlusion. Nay and Barnes[6] observed thirty-seven instances of thromboembolic lesions occurring in 100 patients with acute coronary thrombosis. Hellerstein and Martin,[2] in the most recent review of this subject, report 185 instances

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(12 per cent) of clinical embolism in 1,605 cases of myocardial infarction. Thus, there is ample evidence of the role of intravascular clot formation complicating the occlusive episode and thereby increasing the mortality rate.

Use of Anticoagulants in Acute Myocardial Infarction.—In 1939 Solandt and associates[7] reported that heparin prevented the occurrence of mural thrombi in dogs whose coronary arteries were occluded experimentally. It was not until 1946 that the first of four papers[8-11] was published in which Dicumarol was used in the management of acute myocardial infarction in series of significant numbers. The authors of these papers reported a reduction in the mortality rate and in the number of thromboembolic episodes when Dicumarol was added to the conventional methods of treatment. Nichol and Page, Jr.,[8] used Dicumarol in fifty instances of acute myocardial infarction. There was one case of clinical embolism. No fatalities occurred in the twenty-six patients suffering their first attack. Among the other patients there were eight deaths. Post-mortem examination of six of these cases failed to reveal any mural thrombi, peripheral embolism, or pulmonary embolism. Peters and co-workers[9] reported two deaths in fifty cases of acute coronary thrombosis treated with Dicumarol as compared with a control series of sixty patients treated without Dicumarol in which thirteen deaths occurred. Of the thirteen fatalities, six were due to embolism. Wright[10] used Dicumarol in the management of seventy-six patients with acute myocardial infarction. He found that the mortality was reduced to one-third of that anticipated with conventional therapy. Fifty patients with acute myocardial infarction treated with Dicumarol were compared by Parker and Barker[11] with 100 similar patients not given Dicumarol. They found that the incidence of vascular complications was 4 per cent following Dicumarol therapy and 37 per cent in the control group. The mortality rate was reduced from 13 per cent in the control series to 10 per cent in their series given Dicumarol.

In summary, the number of patients treated with Dicumarol totaled two hundred twenty. There were thirty deaths, or a mortality rate of 14 per cent. This is an excellent result, especially when one takes into account the fact that forty-three of Wright's patients had repeated attacks of coronary occlusion, embolic phenomena, or both (Table I).

TABLE I. RESULTS OF TREATMENT WITH DICUMAROL IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

SOURCES	NO. OF PATIENTS	DEATHS	PER CENT DEATHS
Nichol and Page[8]	44	8	18
Peters, Guyther, and Brambel[9]	50	2	8
Wright*[10]	76	15	20
Parker and Barker[11]	50	5	10
Our series	75	7	9
Total	295	37	12.5

*Forty-six of the cases of Wright's series were deliberately selected because they had complications known to be associated with a high mortality rate. This fact may very well account for the higher mortality rate in his series.

The experience which has been cited constitutes a rational basis for the use of Dicumarol in the management of acute myocardial infarction in an attempt to: (1) prevent further thrombosis in the coronary arteries and to inhibit further extention of the existing thrombus; (2) avert phlebothrombosis, thrombophlebitis, and pulmonary embolism; (3) prevent the formation of a mural thrombus or the extension of already formed thrombi; and (4) prevent peripheral arterial thrombosis.

PURPOSE OF STUDY

In this report we wish to present the results with Dicumarol therapy in relation to the incidence of vascular complications in acute coronary thrombosis and the overall mortality rate in seventy-five consecutive patients. These results are compared with those of a control series consisting of the last 100 patients with acute myocardial infarction managed conventionally on the same service at Lincoln Hospital before the advent of Dicumarol therapy.

ANALYSIS OF PATIENTS

The patients in both the control series and in the series treated with Dicumarol were ward patients at Lincoln Hospital, one of the municipal hospitals of New York City. The subjects were white, Negro, and Puerto Rican patients of the lowest income group, and were admitted to the hospital within the last two and one-half years. All the patients in both series had well-defined clinical, electrocardiographic, and other laboratory evidence of acute myocardial infarction. The management of both series of patients was the same except for the use of Dicumarol in one group. In the series of patients given Dicumarol, the youngest patient was 38 years of age and the oldest, 80 years. The average age was 60 years in the series given Dicumarol as compared with an average age of 58 years in the control series. Table II indicates the distribution as to age, sex, mortality, and thromboembolic complications of the patients in both the control series and the series receiving Dicumarol.

TABLE II. DISTRIBUTION OF SERIES GIVEN DICUMAROL AND CONTROL SERIES ACCORDING TO AGE, SEX, MORTALITY, AND THROMBOEMBOLIC LESIONS

AGE (YEARS)	SEX				MORTALITY				THROMBOEMBOLISM			
	DICUMAROL		CONTROL		DICUMAROL		CONTROL		DICUMAROL		CONTROL	
	M	F	M	F	M	F	M	F	M	F	M	F
30-39	1	0	2	0	0	0	0	0	0	0	0	0
40-49	10	3	16	6	0	1	3	1	0	1	4	1
50-59	18	5	22	10	0	1	5	4	0	1	6	3
60-69	18	8	22	7	0	2	11	5	0	0	4	1
70-79	7	4	8	4	2	1	4	2	0	1	1	1
80-89	1	0	2	0	0	0	0	0	0	0	0	0
90-99	0	0	1	0	0	0	0	0	0	0	0	0
Total Per Cent	55	20	73	27	2	5	23	12	0	3	15	6

In the Dicumarol series, thirty-six patients had had a previous hypertension, twenty-one had had one previous episode of acute myocardial infarction, one had had two previous episodes, and another had had three previous episodes of myocardial infarction. A previous history of angina pectoris was obtained in twenty-five patients. Congestive failure was present in nine cases. Two patients had had previous episodes of cerebrovascular occlusion. There were forty-two instances of anterior myocardial infarction, and thirty-two of posterior myocardial infarction. Nonvascular complications in these patients were: diabetes mellitus in eleven, rheumatic heart disease in two, chronic cholecystitis in two, latent syphilis in two, syphilitic aortitis and syphilitic aneurysm in one, and renal insufficiency, diabetic ketosis, carcinoma of the breast, mixed tumor of the parotid gland, carcinoma of the prostate, and bronchiectasis, each present in one patient.

Contraindications to Dicumarol Therapy.—In the series of patients given Dicumarol no attempt was made to select certain patients because of the mildness or severity of their reaction to the acute myocardial infarction. The contraindications to Dicumarol in the management of acute myocardial infarction were as follows: (1) hypoprothrombinemia due to severe hepatic insufficiency; (2) blood dyscrasias with bleeding tendencies; and (3) ulcerative lesions of the gastrointestinal tract.

It should be remembered that patients receiving quinine[12] or salicylates[13] may have elevated prothrombin times, and that they may show a marked response to the usual dose of Dicumarol. One patient with severe renal insufficiency was treated with Dicumarol in reduced dosage. The only patients with acute myocardial infarction who were not included in either the control series or in the series given Dicumarol were those moribund patients who died within forty-eight hours after admission to the hospital. The reason for their exclusion from either series was the known fact that Dicumarol does not usually cause an effective hypoprothrombinemia before forty-eight hours. The inclusion of such patients in the series studied would not give additional information as to the effectiveness of anticoagulant therapy in acute myocardial insufficiency. There were three such moribund patients who were given one to two doses of Dicumarol and who died within forty-eight hours after admission. These deaths occurred before the prothrombin concentration could be reduced to an effective anticoagulant level. A study of such a series is in progress.

METHOD

Quick's method[14] of prothrombin determination of undiluted plasma was used. Vacuum desiccated rabbit lung served as the thromboplastic agent and was highly satisfactory. The normal prothrombin time was 14 to 16 seconds. Dicumarol was given in order to reduce the prothrombin concentration to between 10 and 30 per cent of normal. The prothrombin was maintained at this reduced concentration throughout the period of complete bed rest. In this method, using rabbit lung as the source of thromboplastin, a prothrombin time of 28 seconds represents a 30 per cent concentration of prothrombin; 35 seconds represents 20 per cent concentration; and 48 seconds represents 10 per cent prothrombin concentration.

In administering Dicumarol every effort was made to obtain an anticoagulant effect in the blood as soon as possible after acute myocardial infarction was diagnosed. Dicumarol was given to the patient according to the following schedule: (1) When the initial prothrombin time was normal, 300 mg. Dicumarol was given to the patient. (2) On the following day, if the prothrombin time was lower than 28 seconds, 200 mg. of Dicumarol was administered; if the prothrombin time was between 28 and 35 seconds, the patient received 100 mg. of Dicumarol; if the prothrombin time was above 35 seconds, Dicumarol was not given. (3) Following the second prothrombin determination, the prothrombin time was taken every forty-eight hours. Dicumarol was given in 50 to 100 mg. doses when the prothrombin time was between 35 and 48 seconds, according to the individual patient's sensitivity to the drug. If the prothrombin time rose above 48 seconds, Dicumarol was not administered. If the prothrombin time went below 28 seconds, larger doses than the maintenance doses of 50 to 100 mg. were given. On the alternate days, when prothrombin determinations were not performed, Dicumarol was given in doses of 50 milligrams. This helped to maintain the prothrombin at an effective anticoagulant concentration without marked alterations in prothrombin concentration from day to day.

If there was any evidence of bleeding, such as microscopic hematuria, purpuric spots in the skin, rectal bleeding, and so forth, Dicumarol was discontinued and 50 mg. synthetic vitamin K (menadione bisulfite) was given intravenously.[15] When the prothrombin time rose above 48 seconds (below 10 per cent prothrombin concentration), Dicumarol was discontinued until the prothrombin concentration returned to an effective anticoagulant level. When bleeding occurred in patients whose prothrombin concentration was below 10 per cent, intravenous synthetic vitamin K controlled the bleeding and increased the prothrombin concentration to above 10 per cent of normal within twenty-four hours. Dicumarol therapy was then resumed.

We have found that patients differ from one another in their response to Dicumarol. The same patient may show variations in sensitivity to the drug at different times. The Dicumarol schedule had to be varied in a number of instances in order to obtain and maintain an effective anticoagulant level. The best example of this is described in the following case report.

CASE 40.—M. E., a 69-year-old white woman, was known to have had diabetes for ten years and hypertensive heart disease for one year. Her diabetes was controlled by diet and protamine zinc insulin. Two weeks before admission the patient had a nasopharyngitis which continued up to the time of admission. One week before admission she became drowsy and the drowsiness increased during the ensuing week. In the last week before admission she developed generalized pruritus and vomited several times daily. On admission her temperature was 100.4° F.; pulse, 110; respirations, 24; and blood pressure was 135/75. Urinalysis and determination of blood carbon dioxide combining power substantiated the diagnosis of diabetes mellitus with ketosis. On admission physical examination revealed the patient's heart to be enlarged. The point of maximum intensity was 2.0 cm. to left of the mid-clavicular line in the fifth intercostal space. The heart sounds were distant and of poor quality. An electrocardiogram revealed an acute anterior infarction. Two hundred milligrams of Dicumarol were given instead of the usual 300 mg. because the initial prothrombin concentration was 40 per cent of normal. With this single dose of Dicumarol the patient's prothrombin concentration reached an effective anticoagulant level in twenty-four hours and remained there for nine days without additional Dicumarol. On the tenth

day the prothrombin concentration rose above the effective anticoagulant level. A second dose of Dicumarol, this time 100 mg., was given. In twenty-four hours the prothrombin concentration was again reduced to an effective anticoagulant level, which was maintained for seven days. At this time, the patient's diabetes was well under control. For the remaining fifteen days that she received Dicumarol, the patient required 50 to 100 mg. every other day in order to maintain an effective prothrombin concentration. Liver function tests were normal. The patient recovered and left the hospital after six weeks with mild angina pectoris on effort.

Complications Arising From Dicumarol Therapy.—The only complication that may occur from the use of Dicumarol is hemorrhage. In our series of seventy-five patients given Dicumarol there were no major hemorrhagic episodes. None of the patients required blood transfusions. Two patients had minor rectal bleeding episodes from internal hemorrhoids when their plasma prothrombin levels dropped below 10 per cent. One patient had a macroscopic hematuria for twenty-four hours. These patients received 50 mg. of synthetic vitamin K (menadione bisulfite) intravenously, and within twenty-four hours the bleeding had ceased. The patients were then continued on Dicumarol therapy, thereafter being maintained closer to a prothrombin concentration of 30 per cent than to 10 per cent. They had no other bleeding episodes, made uneventful recoveries, and were discharged from the hospital. When Dicumarol therapy is guided by prothrombin determinations performed every twenty-four to forty-eight hours, it is our opinion that there is little danger of major hemorrhagic episodes occurring in patients with acute myocardial infarction. We have seen no untoward effects in our series of seventy-five cases, due, as we insist, to careful laboratory control.

RESULTS

In the control series there were twenty-one instances of thromboembolic lesions occurring in the patients with acute myocardial infarction. There were ten instances of pulmonary embolism, four of thrombophlebitis, four of cerebral thromboembolic disease, and three instances of arterial embolism to the leg. The series of patients given Dicumarol included only three instances of thromboembolic disease complicating the acute myocardial infarction after the administration of Dicumarol. There were thirty-five deaths in the control series and seven deaths in the series given Dicumarol. Thus, there was a mortality rate of 9 per cent in the series given Dicumarol as compared with a mortality rate of 35 per cent in the control series. The incidence of thromboembolic lesions was 4 per cent in the series given Dicumarol and 21 per cent in the control series. This is an impressive and significant reduction in the incidence of intravascular thrombosis and in the per cent of fatalities. Three patients in the series given Dicumarol had signs and symptoms of thrombophlebitis before Dicumarol was administered. However, they showed no extension of intravascular clotting after Dicumarol was administered and recovered uneventfully. One patient had a pulmonary embolism following the acute myocardial infarction. He was then placed on Dicumarol. No further episodes of embolism occurred, and he recovered uneventfully. One patient suffered a cerebral embolism with hemiplegia as a complication of an acute coronary occlusion. He was then placed on

Dicumarol and there were no recurrences of thromboembolic episodes. He left the hospital with moderate paresis of the right arm and right leg.

Analysis of the Mortality Group.—In the clinical analysis of the seven deaths that occurred in this series of seventy-five cases given Dicumarol, it was found that three patients died of marked congestive heart failure, two in the convalescent period, within a month, and one at the end of seventh week; two patients died of cerebral thrombosis; one patient died of uremia; and one patient died suddenly twenty-seven days after the acute myocardial infarction. The latter episode was probably due to ventricular rupture with acute pericardial tamponade. The patient was a 70-year-old man who had a two-year history of hypertension. His course in the hospital was uneventful until the twenty-seventh day following the acute coronary occlusion. While eating his evening meal, he suddenly became comatose. He could not be aroused. His heart sounds were very rapid and distant and ceased one minute after he lost consciousness. The two patients who died of cerebral thrombosis were women. Both were diabetic patients of long standing, which was rather significant in the evaluation of the intercurrent lesion. Their case reports follow.

CASE 27.—M. E., a 48-year-old Negro woman, had had hypertensive heart disease for nine years and diabetes mellitus for five years. She had had three previous episodes of acute myocardial infarction. Five hours before admission the patient had a crushing substernal pain which radiated into the right shoulder and right arm and was not relieved by nitroglycerin. On admission her temperature was 99.5° F.; pulse, 100; respirations, 24 per minute; and blood pressure was 170/110. The heart sounds were distant and the heart was enlarged to the left. The point of maximum intensity was on the anterior axillary line in the sixth intercostal space. A diagnosis of acute myocardial infarction was made. An electrocardiogram revealed an acute posterior infarction. She was started on 300 mg. of Dicumarol and ninety-six hours later her prothrombin concentration was at an effective anticoagulant level of 30 per cent. This was seven days after the occlusion. On her eighth hospital day she became irrational, disoriented, and submaniacal. On the twelfth day a mild right facial weakness was first noticed. This gradually increased in severity. Three days later a concomitant left hemiplegia developed. Her field of consciousness slowly narrowed; disorientation increased; she became semicomatose and expired seven days later. The administration of Dicumarol, therefore, could not be continued regularly or effectively.

CASE 32.—R. E., a 72-year-old white woman, had had mild diabetes mellitus for thirty years. There was no history of hypertension. Her diabetes was controlled on diet alone. Four years before the present admission, she had been hospitalized for an acute myocardial infarction. Two years before admission she developed a cerebral thrombosis and was hospitalized for ten weeks. She still had right facial weakness and paresis of the left hand at the time of this admission. For the previous nine months she had been taking daily rations of digitalis for her failing heart. The patient was admitted to the hospital because of a three-day history of severe pressing substernal pain, radiating to the left shoulder and left arm. On admission her temperature was 102° F.; pulse rate, 102; and ventricular rate, 120 per minute; respirations, 28 per minute; and blood pressure, 110/60. Examination of the heart revealed it to be normal in size. The sounds were distant and poor in quality, and auricular fibrillation was present. The electrocardiogram revealed a recent posterior myocardial infarction. She was started on 300 mg. of Dicumarol on the second hospital day. On the fifth hospital day when the prothrombin concentration had reached an effective anticoagulant level of 30 per cent for the first time, the patient developed paresis of the left arm. She did not complain of headache nor was there evidence of nuchal rigidity. The mild disorientation which was present prior to this episode increased rapidly, so that Dicumarol could not be administered effectively. Her chest film revealed a heart of normal size. Her blood pressure at this stage was 150/80. She died on the twelfth hospital day.

Comment: Both cases (M. E. and R. E.) had previous acute coronary occlusions in addition to long-standing diabetes mellitus. In Case 32, R. E., the prothrombin concentration reached 30 per cent the same day on which the cerebral lesion developed. If the cerebral thrombosis had not occurred at the time it did, it is possible that it might have been prevented once the effective prothrombin level had been established. However, it probably would have then occurred soon after the prothrombin concentration was allowed to return to normal. In Case 27, M. E., the prothrombin was not at an effective anticoagulant level until the seventh day following the acute coronary occlusion. It is very likely that in this case, also, the cerebral lesion developed on the same basis. The effective prothrombin level had hardly been established in either case when these lesions developed. The similarity in the course of both these diabetic patients is worthy of note.

Permission for autopsy was not obtained in the seven patients in the Dicumarol series who died. A post-mortem examination was performed, however, on Case 22, F. L., a 55-year-old white man who had an acute anterior myocardial infarction, syphilitic aortitis, and a syphilitic aneurysm of the ascending aorta. He recovered from his acute occlusive episode and was discharged from the hospital after six weeks, only to be readmitted one month later in marked congestive heart failure. He died after forty-eight hours, despite therapy. Post-mortem examination revealed an enlarged heart weighing 500 grams. There was hypertrophy and dilatation of the left ventricle, with marked atherosclerosis and narrowing of the left anterior descending coronary artery. There was an almost completely healed myocardial infarct in the anterior wall of the left ventricle. There was no evidence of mural thrombi, ventricular aneurysm, pulmonary embolism, or any systemic thromboembolic lesions.

In the control series post-mortem examinations were performed on nine patients. In examination of these nine patients, five instances of pulmonary embolism, five instances of peripheral thromboembolic lesions, and four mural thrombi were found.

DISCUSSION

Askey and Neurath[16] reported that digitalis was contraindicated in acute myocardial infarction. They found that though the danger of sudden death from myocardial rupture or from ventricular fibrillation was not significantly increased when digitalis was used, there was a marked rise in the incidence of clinical embolism. They reported thirty-one deaths in thirty-two patients with acute myocardial infarction complicated by congestive heart failure with auricular fibrillation and treated with digitalis. In thirteen of these thirty-one patients, death was due to arterial embolism. Peters and associates[9] reported nine deaths, most of them due to embolism, in seventeen patients with acute myocardial infarction complicated by congestive heart failure and treated with digitalis. In their series of fifty patients with acute myocardial infarction treated with Dicumarol, there were eight patients with congestive heart failure who required digitalis therapy. Only one of these eight patients died. Thromboembolic lesions did not occur in any of these patients.

The findings in our study conform with those of Peters and co-workers.[9] In our control group of 100 patients with acute myocardial infarction, seventeen required digitalis for congestive failure. Nine (53 per cent) of these seventeen patients died. Of these nine patients, five had signs of embolism. In the series treated with Dicumarol there were fifteen patients with congestive heart failure severe enough to require digitalis. Three of these (20 per cent) died in marked congestive failure with no signs of thromboembolic complications.

If digitalis increases the coagulability of the blood, as stated by De Takats and associates,[17] Massie and co-workers,[18] and Peters and associates,[9] then the results obtained by us and by others[9] in small groups of patients with acute myocardial infarction complicated by congestive heart failure and treated with digitalis without the occurrence of thromboembolic lesions suggest that Dicumarol can oppose effectively the thrombogenic property of digitalis which increases the tendency for embolism. We feel Dicumarol should be administered to patients with acute myocardial infarction who are in congestive failure and are receiving digitalis.

SUMMARY

Dicumarol was used in the management of seventy-five consecutive ward patients with acute myocardial infarction. The mortality rate was 9 per cent and the incidence of thromboembolic lesions was 4 per cent. These results reveal a decided improvement over the results obtained in a control series of 100 patients with acute myocardial infarction treated with conventional therapy. In the latter series there was a mortality rate of 35 per cent and an incidence of thromboembolic lesions of 21 per cent. There were no serious complications attributable to the use of Dicumarol.

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Clinical Reports

NEOPLASTIC METASTASIS TO THE HEART*

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METASTATIC involvement of the heart by tumor growth is not too infrequent. Statistical studies of large series of autopsies by several authors indicate an incidence varying from 0.24 to 1.06 per cent.[1-5] The largest series of cases reported in the literature is that of Scott and Garvin[2] who found 118 instances of metastatic involvement of the heart in 1,082 cases of malignant disease in a series of 11,000 autopsies at Cleveland City Hospital during a period of twenty years. They stated that "metastasis to the heart occurred from neoplasms involving practically every organ of the body."

Comprehensive reviews of the reported cases in the literature were made by Yater[6] in 1931 and by Lisa and his associates[7] in 1941 and will not be repeated here. The purpose of the present paper is to record an instance of an unusually extensive involvement of the heart by metastatic tumor in a case of malignant melanoma; in addition, five other cases of invasion of the heart by secondary metastases are briefly described.

CASE REPORTS

CASE 1.—A 48-year-old white man was admitted to the hospital on Dec. 13, 1946, complaining of daily chills, fever, and sweating accompanied by soreness and aching pains in the muscles, joints, and bones for the past six weeks; the bones felt as if they were "bursting." Two years prior to admission a black mole on the left wall of the chest was removed with an "acid solution." The wound healed and there was no apparent local recurrence. He was well until six weeks before admission when he was taken ill with a sudden chill followed by fever and sweating, and accompanied by aching pains in the muscles, joints, and bones. He had marked anorexia but no nausea or vomiting. These symptoms had recurred almost daily, and increased gradually in severity; at times he was delirious. Three weeks before admission a tender "spot" developed in the right upper quadrant of the abdomen; two weeks before admission he noticed tarry stools, and one week before admission he developed a cough productive of blood streaked sputum.

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The patient was poorly nourished and appeared to be acutely and chronically ill. Numerous small, hard nodules were palpable in the subcutaneous tissues over the entire body surface; many of these nodules appeared bluish in color. The supraclavicular nodes were moderately enlarged and tender. There was generalized muscle tenderness. The heart was not considered to be enlarged, the rhythm was regular, rate 116 per minute, and the sounds were of good quality; a faint systolic murmur was heard over the base; the blood pressure was 108/64. The liver was palpated 6.0 cm. below the costal margin and was very tender; there was generalized tenderness of the entire abdomen but no other organs or masses were noted. Roentgen examination of the chest revealed slight enlargement of the cardiac shadow. Complete blood count revealed 3,740,000 red blood cells, 16,250 white blood cells, 13.6 grams of hemoglobin, 85 per cent polymorphonuclear leucocytes, 10 per cent lymphocytes, 4 per cent monocytes, and 1 per cent basophiles. Urinalysis showed 0 to 2 white blood cells, 1 to 3 red blood cells per high-power field, and a few waxy, hyaline, and granular casts. The blood Kahn reaction was negative. The diagnosis of malignant melanoma with generalized metastases was made. Biopsy of one of the subcutaneous nodules confirmed this diagnosis.

The patient's temperature fluctuated between 98 and 101°F., and at times reached 104 °Fahrenheit. The blood culture was negative; a blood smear did not show malarial parasites. No acid-fast bacilli were found in the sputum. Agglutination tests for typhoid, paratyphoid, brucellosis, and tularemia were negative.

The patient's heart rate was rapid and fluctuated between 98 and 134 per minute, the higher rates occurring coincidentally with the rises in temperature. The anemia and weakness gradually increased in severity and the patient died on Dec. 26, 1946, thirteen days after admission to the hospital.

Necropsy.—Widespread nodular metastases were found in the lungs, pleura, heart, liver, gall bladder, spleen, pancreas, adrenals, kidneys, ureters, urinary bladder, prostate, testes, thyroid, brain, bones, lymph nodes, peritoneum, mesentery, serosa of the gastrointestinal tract, and diaphragm.

The pericardial cavity contained approximately 200 c.c. of clear straw-colored fluid. The pericardium itself presented no abnormalities. The heart weighed 550 grams. The surfaces of the heart were studded with conglomerated nodular infiltrations which varied from pinkish-white to grayish-white in color. The endocardial surfaces of the auricles and ventricles were extensively infiltrated with conglomerate masses of variously sized nodules involving all of the musculi pectinati, trabeculae carneae, and papillary muscles. These infiltrations were more marked in the right chambers (Fig. 1). A few nodules were seen scattered over some of the chordae tendineae and the leaflets of the mitral and tricuspid valves. The cusps of the pulmonic and aortic valves appeared normal. The foramen ovale was closed. On section, the wall of the left ventricle measured 2.8 cm. and that of the right ventricle, 1.0 cm. in thickness; the cut surfaces were pinkish-brown in color, friable, and extensively infiltrated by variously sized tumor nodules which appeared grayish in color. The ostium of the right coronary artery presented sclerotic plaques; the coronary vessels were patent throughout their entire course. The aorta presented numerous sclerotic plaques, but its elasticity was fairly well preserved.

Microscopic examination of several sections taken from the interventricular septum, left and right ventricles, and auricles showed diffuse and extensive involvement of the epicardium, myocardium, and endocardium by tumor growth. The tumor cells were arranged in solid nodular masses and columns more or less completely replacing the cardiac muscle in many areas. In the relatively uninvolved zones the cardiac muscle bundles showed fragmentation, indistinct striations, replacement fibrosis, and a moderate degree of congestion and edema. Many venous and lymph vessels were seen to contain tumor cells. The tumor cells were fairly uniform in appearance; they presented large vesicular nuclei surrounded by a varying amount of faintly staining eosinophilic cytoplasm; many mitotic figures were noted. No melanin pigment was seen in these cells (Figs. 2 and 3).

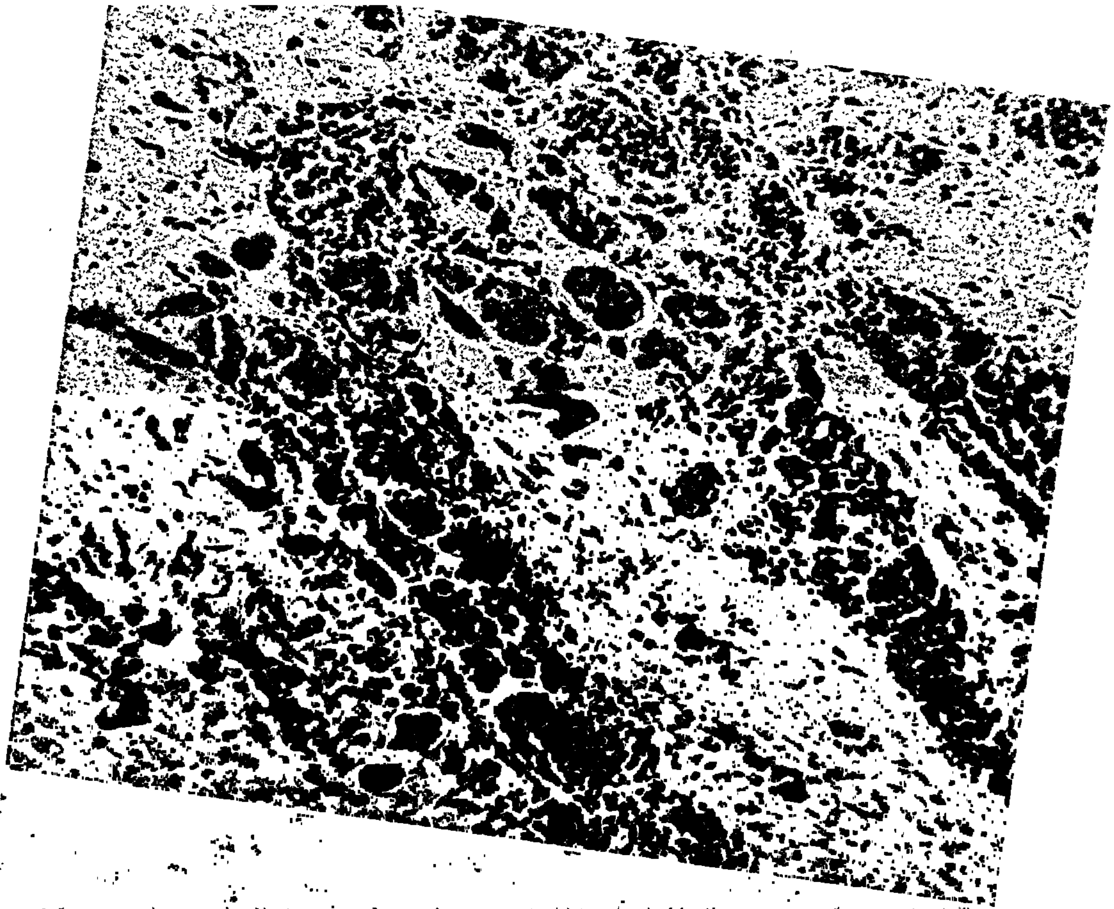
CASE 2.—A 39-year-old white man in 1940 noted a small, dark "birthmark" just below the left axilla; this grew in size slowly so that his clothes irritated it causing it to bleed. The growth

was fulgurized by his physician in 1942. In October, 1945, he noted a small swelling in the left axilla. In July, 1946, small nodules appeared over the entire body; the patient began to lose weight, became weak, and noted shortness of breath. He applied for admission to the hospital on Oct. 26, 1946, because two days previously his right arm and right leg had become weak and lifeless.

Fig. 1.—Case 1. Open right ventricle. Note the diffuse nodular involvement of all parts of the heart.

Numerous subcutaneous nontender nodules were found distributed over the entire body surface; the skin over some of these nodules appeared purplish in color. The heart was not enlarged; the rhythm was regular, the rate 72 per minute, and no murmurs were audible. The blood pressure was 120/76. The liver was nodular, slightly tender, and was felt three fingerbreadths below the costal margin. There was spastic paralysis of the right upper and lower extremities with hyperactive reflexes and positive plantar reflex. Roentgen examination of the chest showed multiple nodular infiltrations throughout both lung fields; the heart was not enlarged.

On the evening of October 29 the patient had a sudden clonic seizure involving the right upper and lower extremities followed by loss of consciousness and stertorous breathing. The entire episode lasted approximately two hours. On the following morning the patient was conscious and alert, but a slight hesitancy in his speech was observed and he had difficulty in choosing the proper words. His condition gradually deteriorated and he died on Dec. 4, 1946. During the period of hospitalization the temperature remained between 98 and 99°F. with occasional rises to 101°F. in the evening. The heart rate varied between 80 and 100 per minute with occasional rises up to 110 and 116. At no time was any definite evidence of cardiac failure noted.



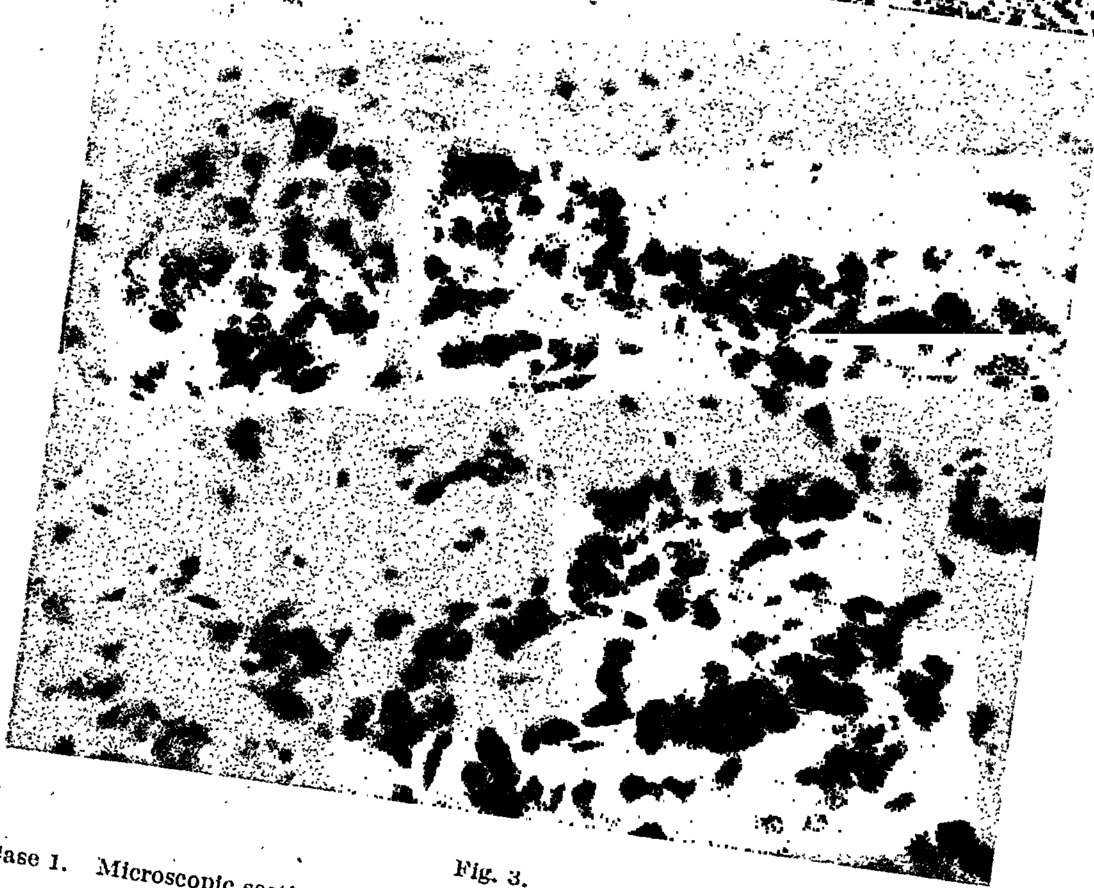


Fig. 3.

Fig. 2.—Case 1. Microscopic section of wall of the left ventricle (medium power). Note the nodular and columnar arrangement of the invading tumor cells.

Fig. 3.—Case 1. High-power view of section from the interventricular septum. Note the uniform appearance of the tumor cells.

Necropsy.—Numerous subcutaneous nodules, varying in size from match-head to 3.0 cm. in diameter, were distributed throughout the entire body surface. The skin over most of these nodules appeared brownish-blue. Nodular metastases were found in the lungs, pleura, heart, liver, pancreas, adrenals, kidneys, brain, peritoneum, mesentery, and lymph nodes. The heart weighed 260 grams; several tumor nodules of varying size were found in the walls of both auricles and the left ventricle. Histologic examination showed malignant melanoma.

CASE 3.—A 52-year-old white man was well until March, 1946, when he developed "pneumonia." Bronchoscopic examination revealed inoperable cancer in the left lung. In July, 1946, he coughed up "pus and blood" during a period of three weeks. In September, 1946, he began to have pains in the left hip and both shoulders. Around December, 1946, he noted a small, hard nodule in the left testicle. In January, 1947, multiple subcutaneous, hard, tender nodules appeared all over his body. In March, 1946, he began to lose weight and strength, the loss amounting to about 60 pounds in weight. His stools had been black off and on since April, 1946.

On admission to the hospital on Jan. 28, 1947, the patient appeared extremely ill and weak. Numerous subcutaneous tumor nodules were scattered over the entire body surface. There were flatness and absent breath sounds over the entire left lung. The heart was not enlarged. The rhythm was regular, the rate, 94 per minute. A systolic murmur was heard over the apex and pulmonic area. The blood pressure was 106/60. The liver was felt three fingerbreadths below the costal margin. A large, hard, firm tumor mass measuring 8.0 to 9.0 cm. in diameter was present in the left testicle. The scrotal skin presented a bluish discoloration. There was generalized adenopathy in the axillary, supraclavicular, and inguinal areas. Roentgen examination of the chest showed a homogeneous density occupying the entire left chest, displacement of the mediastinum toward the left side, and marked distention of the right lung. Bronchoscopy showed a tumor mass attached to the posteroinferior wall of the left primary bronchus about 2.0 cm. below the carina occluding the lumen. Histologic examination of tissue removed from this tumor showed only necrotic tissue. Histologic examination of one of the subcutaneous nodules showed an undifferentiated type of tumor resembling testicular tissue in appearance and cellular arrangement.

The temperature fluctuated between 98 and 99°F. with occasional rises up to 100° Fahrenheit. The heart rate varied between 84 and 110 per minute, occasionally rising to 120 per minute. The patient did not respond to symptomatic therapy; his debility gradually increased, and he died on Feb. 21, 1947.

Necropsy.—Numerous subcutaneous tumor nodules were scattered over the entire body surface. The left main bronchus was completely occluded by a tumor mass, and multiple abscesses were present in the left lower lobe. There was tumor invasion of the posterior mediastinum with necrosis and perforation of the esophagus and abscess formation in the mediastinum. A large tumor mass was attached to the left testicle. Tumor nodules of varying sizes were found in the adrenals, kidneys, walls of the small and large intestines, and retroperitoneal fat. The heart weighed 310 grams; the epicardial surface was covered by a shaggy fibrinous exudate and adhesions were present between the parietal and visceral layers of the pericardium. The pericardial cavity contained approximately 150 c.c. of cloudy, greenish fluid. A few grayish-pink, small tumor nodules were scattered through the wall of the left ventricle.

Histologic examination showed embryonal carcinoma with lymphoid stroma of the left testicle.

CASE 4.—A 54-year-old white man "bruised" a birthmark above the left ankle in 1942. The lesion was excised in 1943. Local recurrence and two small masses in the thigh along the course of the saphenous vein were removed in 1944. Excision of local recurrence, followed by skin graft, was performed in 1946. In October, 1946, a mass appeared beneath the graft. Bioposy of this mass at another hospital showed malignant melanoma, and amputation below the knee was performed on Oct. 31, 1946. In January, 1947, tender subcutaneous nodules appeared over the entire body, and the patient began to complain of continuous griping pains in the abdomen and of difficulty in getting his breath. He was admitted to the hospital on March 20.

Numerous subcutaneous tender nodular masses were found distributed over the entire body surface. The heart was not enlarged; the rhythm was regular and the rate, 88 per minute. No

murmurs were heard and the blood pressure was 148/96. There was diffuse tenderness on pressure over the abdomen; the liver was palpable, the edge being smooth. Roentgen examination of the chest showed nodular metastases in the left upper, left lower, and right lower lobes. The transverse diameter of the heart was 15.5 cm. and the intrathoracic diameter was 30 centimeters.

The patient was treated with methyl-bis (B-chloroethyl) amine hydrochloride; he was given 6.0 mg. intravenously (0.1 mg. per kilogram of body weight) every other day for four doses. However, he gradually became weaker and died on April 11, 1947. During the period of observation the temperature at first fluctuated between 98.6 and 101°F.; later the changes became wider and fluctuated between 97 and 102° Fahrenheit. The pulse rate varied between 72 and 110 per minute, rising occasionally to 120 coincidentally with the elevated temperature peaks.

Necropsy.—Subcutaneous nodular masses were found distributed throughout the entire body surface and nodular metastases were found in the lungs, heart, liver, adrenals, kidneys, gastrointestinal tract, and brain. The heart weighed 380 grams; isolated tumor nodules were found in the walls of both auricles, both ventricles, and interventricular septum, and one nodule was present at the base of the tricuspid valve. Microscopic examination showed malignant melanoma.

CASE 5.—A 60-year-old white man was admitted to the hospital on May 19, 1947. For the past fifteen to twenty years he had had a slight cough productive of small amounts of sputum. In 1942 he developed weakness, malaise, and easy fatigability. In 1945 his cough became worse; the sputum increased in amount and occasionally was streaked with blood. In the summer of 1946 radiologic examination of the chest showed tuberculosis in the left upper lobe and "some disease" in the right lung; the sputum, however, did not show tubercle bacilli. In September, 1946, the patient developed a constant pain in the right lower chest. In February, 1947, tuberculous lesions in both apices (positive sputum) and a solid tumor in the right lower lobe were found at another hospital where the right lower lobe was removed in March, 1947. Histologic examination was reported to show undifferentiated bronchogenic carcinoma and tuberculosis.

The patient was poorly nourished. There was a draining sinus in the right fifth intercostal space anteriorly. There were decreased expansion, flatness, and absent breath sounds over the lower one-half of the right chest. The heart was not enlarged; the rhythm was regular, the rate, 88 per minute. The sounds were of good tonal quality. The blood pressure was 126/82. Roentgen examination of the chest showed a fluid level in the right chest at the level of the second rib anteriorly, an area of irregular density in the upper part of the right lung field, and scattered areas of density in the upper one-third of the left lung.

Underwater drainage through the sinus in the right chest wall was instituted. Air was seen to escape during coughing, indicating a bronchopleural fistula. During bronchoscopy the bronchopleural fistula was seen through the stump of the open right lower lobe bronchus. Tissue removed from the orifice of the right upper lobe bronchus did not show tumor cells on histologic examination. On May 26 the patient developed a transient right hemiplegia. He gradually became weaker and died on June 21, 1947. The temperature fluctuated between 97 and 99°F. with occasional rises up to 100.2° Fahrenheit. The heart rate at first fluctuated between 80 and 90 per minute; during the last two weeks of the patient's life the rate varied between 90 and 100 per minute; occasionally it rose to 120 per minute coincidentally with the rises in the temperature. At no time was circulatory failure noted.

Necropsy.—The heart weighed 360 grams; grayish-white tumor nodules were present in the wall of the right auricle and interventricular septum varying from 1.2 to 2.5 cm. in diameter. The primary bronchus of the right lower lobe 7.0 cm. distal to the bifurcation of the trachea ended abruptly in a tumor mass measuring 10 cm. in diameter. Several multiloculated cavities filled with cheesy, gray material were present in the left upper lobe. Both adrenal glands were almost completely replaced by tumor; multiple tumor nodules of varying sizes were present in the lungs, both kidneys, small intestines, mesentery, lymph nodes, and the brain. The right pleural cavity contained several multiloculated encapsulated empyema cavities filled with thick, yellow, creamy pus. Histologic examination showed bronchogenic carcinoma, squamous type, and fibrocaseous tuberculosis.

Fig. 4.—Case 6. External appearance of heart. Note the large, variously sized, darkly pigmented nodules.

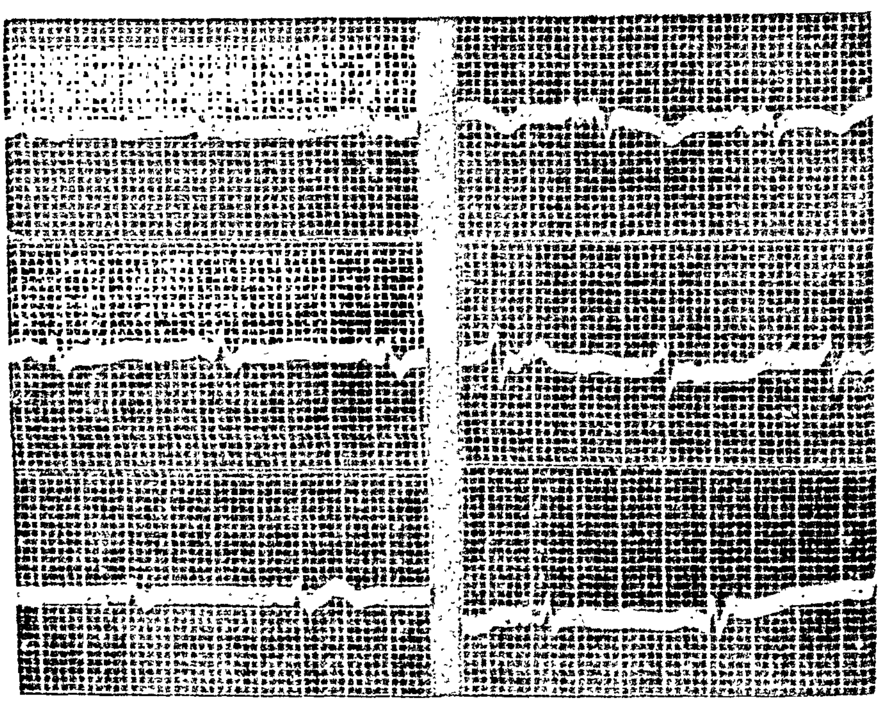


Fig. 5.—Case 6. Electrocardiogram. See text for description.

CASE 6.—A 55-year-old white man was admitted to the hospital on Sept. 18, 1946. In 1939 he began to have pain in the right eye. His doctor treated him for glaucoma. The pain subsided, but the patient lost vision in the right eye. In 1943 exophthalmos of the right eye was noted. Intermittent episodes of pain and swelling of the right eye then followed.

There was marked exophthalmos of the right eye; the bulbar and palpebral conjunctivae were markedly injected. A doughy, tender mass, about one inch long and one-half inch wide, was palpable temporally behind the lower lid; smaller but firmer masses were felt in both fornices which greatly limited movement of the eye. The pupil was small and fixed; the lens showed a cataract. The left eye was normal. The heart was not enlarged; the rhythm was regular, the rate, 72 per minute. No murmurs were audible. The blood pressure was 135/84. Roentgen examination of the chest revealed no abnormalities. The diagnosis of right intraorbital tumor was made and the right orbit was exenterated on Oct. 15, 1946. Histologic examination revealed malignant melanoma.

The patient gradually became cachectic. Subcutaneous nodules appeared all over his body and the liver became enlarged and nodular. Between July 10 and July 23, 1947, he received radiation therapy for palliation. This was of no avail and he died on July 24, 1947. The temperature was at normal levels with only occasional rises up to 100.6° Fahrenheit. The heart rate fluctuated between 72 and 110 per minute with an average rate of approximately 86 per minute. No murmurs were heard nor evidences of circulatory insufficiency noted. The electrocardiogram, taken about four hours before death, showed low voltage of all complexes in all leads, slurring of the QRS complexes in all leads, inversion of T waves, and depression of S-T in Leads CF_2 and CF_4 (Fig. 4).

Necropsy.—Numerous subcutaneous tumor nodules were found over the entire body surface. Discrete nodular metastases were present in the heart, pericardium, pleura, right lung, liver, spleen, pancreas, left adrenal, right kidney, renal pelves, ureters, urinary bladder, gastrointestinal tract, brain, and lymph nodes. The heart weighed 300 grams. Several large, bluish-gray tumor nodules were present in the pericardium, the myocardium of both auricles, the ventricles, and the interventricular septum. A large nodule measuring 4.0 cm. in diameter extended through the entire thickness of the interventricular septum.

The pertinent clinical and post-mortem data are summarized in Table I.

COMMENT

In Case 1 the extensive involvement of the heart muscle at necropsy was so extraordinary that the case aroused great interest. Clinically, during the patient's life no clue was found which indicated possible invasion of the heart by tumor. The only significant abnormal finding referable to the heart was the persistent tachycardia. This was thought to be secondary to the febrile course. The significance of enlargement of the heart as shown by x-ray examination was overlooked.

The varied and bizarre symptomatology and physical findings noted in the cases which have been reported are readily accounted for by the widespread metastases which in some instances involved almost every organ in the body. Of interest was the observation that metastatic involvement of the heart, which in some cases was so extensive that the major portion of the cardiac muscle was replaced by tumor, produced few or no symptoms directly referable to the heart. Similar observations have been made by previous investigators.[6-8] This explains the fact that so few instances of invasion of the cardiac muscle by tumor had been diagnosed ante mortem. In the rare instances the correct diagnosis was made because the tumor growth, either by its sheer size

TABLE I. SUMMARY OF SIGNIFICANT FINDINGS

CASE	RHYTHM AND RATE	ENLARGEMENT OF HEART	BLOOD PRESSURE	MURMURS	CARDIAC FAILURE	ECG	HEART WEIGHT (GM.)	EXTENT OF CARDIAC METASTASES	DIAGNOSIS
1	Regular 96-134	Moderate	108/64	Faint systolic at base	No	——	550	Extensive invasion of walls of all chambers	Malignant melanoma
2	Regular 80-116	No	120/76	None	No	——	260	Nodules in walls of both auricles and left ventricle	Malignant melanoma
3	Regular 84-120	No	106/60	Systolic at apex and at pulmonic area	No	——	310	Small nodules scattered through wall of left ventricle	Embryonal carcinoma of left testicle with lymphoid stroma
4	Regular 72-120	Slight	148/96	None	No	——	380	Nodules in walls of both auricles, ventricles and interventricular septum	Malignant melanoma
5	Regular 80-120	No	126/82	None	No	——	360	Nodules in wall of right auricle and interventricular septum	Bronchogenic carcinoma of right lobe bronchus
6	Regular 72-110	No	135/84	None	No	Low voltage of all complexes; slurring of QRS, inversion of T in CF_2 and CF_4	300	Nodules in walls of all chambers and interventricular septum	Malignant melanoma

or strategic location, produced bizarre and otherwise unexplainable symptoms and physical signs such as intense cyanosis, dyspnea, murmurs which varied in character and intensity with changes in body positions, intractable cardiac failure, arrhythmias, heart block, electrocardiographic abnormalities, unusual or irregular cardiac contour on radiologic examination, and sanguineous and recurring pericardial effusions.[8-10]

The six cases which form the basis of this report also were diagnosed only post mortem.

Analysis of the clinical findings in the cases reported in this communication and those reported in the literature, which are suitable for analysis, reveals the fact that the chief reason for failure to arrive at the correct diagnosis was the absence of any characteristic symptom or sign which would have called attention to the heart. In addition, it may be added, as Fishberg[10] has stated, that "in most of these, it is true, as little attention was devoted to the accurate study of the cardiovascular system as is usually accorded in patients suffering from advanced malignant disease." Tachycardia, otherwise unexplained, was the only constant abnormal finding. The electrocardiogram was likewise of no help. The abnormalities noted in the electrocardiograms[10,12] in most of the cases found in the literature consisted, as in one of the cases reported in this paper, of nonspecific changes such as low voltage complexes, depressed S-T interval, T-wave inversion, and various forms of heart block.

On the basis of these findings one is justified in stating that cardiac metastasis should be thought of in any patient who has malignant disease elsewhere in the body if tachycardia of unexplained origin is present, even if there are no other signs or symptoms which would indicate invasion of the heart. If, in addition, one or more of the abnormal cardiac signs and symptoms which we have listed develop, the diagnosis of metastatic invasion of the heart can be made with reasonable certainty.

SUMMARY

1. A case of extraordinary metastatic invasion of the heart secondary to malignant melanoma is reported. In addition, five other instances of cardiac invasion by metastatic tumor growth are briefly described.

2. The only constant abnormal physical finding noted referable to the heart during life was a persistent tachycardia which was otherwise unexplained.

3. It is believed that the diagnosis of metastatic invasion of the heart by neoplasm can be made with reasonable certainty if an otherwise unexplained persistent tachycardia is present in a patient suffering from malignant disease elsewhere in the body.

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SUPERNORMAL PHASE OF INTRAVENTRICULAR CONDUCTION

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THE law of rest and recovery governs the property of conduction in the heart and explains most of its disturbances. Thus, in cold-blooded and in mammalian hearts, the conduction time is optimal after a longer pause and becomes prolonged if the recovery time is shortened. Occasionally exceptions to this rule have been observed. One such exception is that the second impulse in a series of regularly conducted impulses appearing after a long pause exhibits an abnormal conduction pattern. The explanation offered is that the first impulse appearing after a longer pause is followed by a particularly prolonged refractory period so that the subsequent impulse finds the conduction tissue in a less favorable state of recovery.[10]

Another explanation for exceptions to the rule which has just been stated utilizes the concept of the supernormal phase of recovery. Originally found in nerve and muscle fibers,[2] it was also observed in the heart under certain conditions.[1,3] This supernormal phase of excitability and contractility which follows the relative refractory phase seems to exist in a very slight degree in normal nerve and muscle tissues, but is markedly pronounced in excised nerve and muscle fibers under abnormal conditions. Many observations show that the supernormal phase is closely related to and coincides with the phase of the negative after-potential.

A series of clinical observations was published in which abnormalities of conduction were interpreted as being due to the supernormal phase. Obviously no tests with threshhold stimuli were possible in man; therefore, the evidence is based solely on the interpretation of unusual tracings.[6-9,11] Such tracings were rather rare and always concerned auriculoventricular conduction. Some of the published cases of a supernormal phase of conduction in partial auriculoventricular block were interpreted as being due to the interference between automatic and conducted beats. Therefore, the description of an unusual electrocardiogram which can be explained by the existence of a supernormal phase of *intra*ventricular conduction seems fully warranted.

OBSERVATION

A 56-year-old, very obese woman was hospitalized for painful swelling of the wrists, the small joints of both hands, and the right knee. A similar episode

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of joint swellings had occurred ten years previously. The present complaints were of two weeks' duration.

Examination revealed the involved joints to be red, swollen, and tender. Both ankles showed slight pitting edema. The blood pressure was 180/110. The temperature was 102° Fahrenheit. Clinical examination of the heart disclosed a moderate enlargement of the left ventricle and soft systolic murmurs over the apex and aorta. Moist râles were present in both lung bases. Possibly as a result of the obesity, the liver edge could not be palpated. Roentgen examination revealed enlargement of the left ventricle, a normal aorta, and evidence of pulmonary congestion.

Laboratory studies showed moderate albuminuria without other disturbance of kidney function. A slight glycosuria appeared for a few days. The blood sugar was 150 mg. per cent but soon fell to 89 mg. per cent and remained at approximately this level. The blood count showed 15,000 leucocytes and normal differential and erythrocyte counts. During the first week the erythrocyte sedimentation rate varied between 116 and 126 mm. in one hour, thereafter, gradually becoming normal.

A provisional diagnosis was made of acute rheumatic fever with hypertension of unknown origin and mild diabetes mellitus. There was no evidence of a mitral valvular lesion of rheumatic etiology. Under salicylate therapy the joint changes disappeared within two weeks. The patient also received digitalis in a dose of 0.3 Gm. daily until she developed a 2:1 A-V heart block. The pulmonary congestion rapidly disappeared. The patient was discharged as improved.

The electrocardiogram taken on admission (Fig. 1,*A*) exhibits a left axis deviation, a rate of 82 per minute, and a P-R interval of 0.18 second. The high R wave and short S wave in the chest lead over the left ventricle are suggestive of left ventricular hypertrophy. Fig. 1,*B* was obtained nineteen days later when the patient was markedly improved. It reveals the pattern of left bundle branch block. The P-R interval is prolonged to 0.24 second and the rate is increased to 94 per minute. Chest lead CR_4 does not show the expected delay of the appearance of the intrinsic wave over the left ventricle. This may be due to the fact that the electrode in this instance was still over the right ventricle.

Nine days later a 2:1 A-V block was registered in addition to the bundle branch block. The P-R interval of the conducted beats was still 0.24 second. At this time the dose of digitalis had been reduced from 0.3 to 0.2 Gm. daily. Eight days later the tracing shown in Fig. 2 was obtained and will be described in detail presently. On the next day and during the following two weeks a sinus rhythm with left axis deviation was registered with marked digitalis effect on the RS-T segment and T wave visible in all leads. There was no bundle branch block and no A-V heart block.

Fig. 2 shows the electrocardiogram which is of most interest. The basic auricular rhythm is a sinus rhythm with a rate of approximately 68 per minute. An auriculoventricular conduction disturbance exists in which the P-R interval becomes increasingly prolonged until every fourth to eighth ventricular beat is dropped. We are, therefore, dealing with Wenckebach periods, which are com-

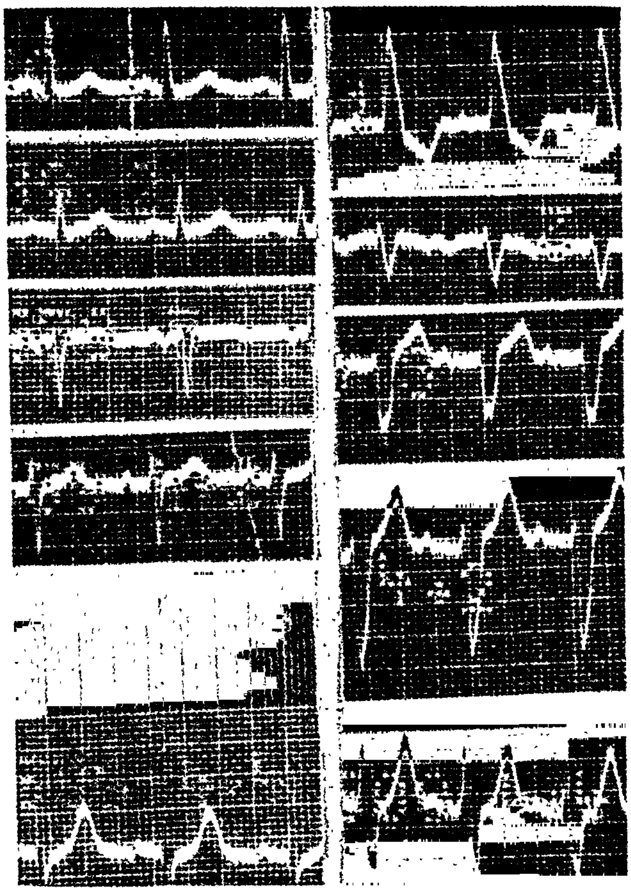

Fig. 1.—*A*, Left axis deviation. *B*, Left bundle branch block.

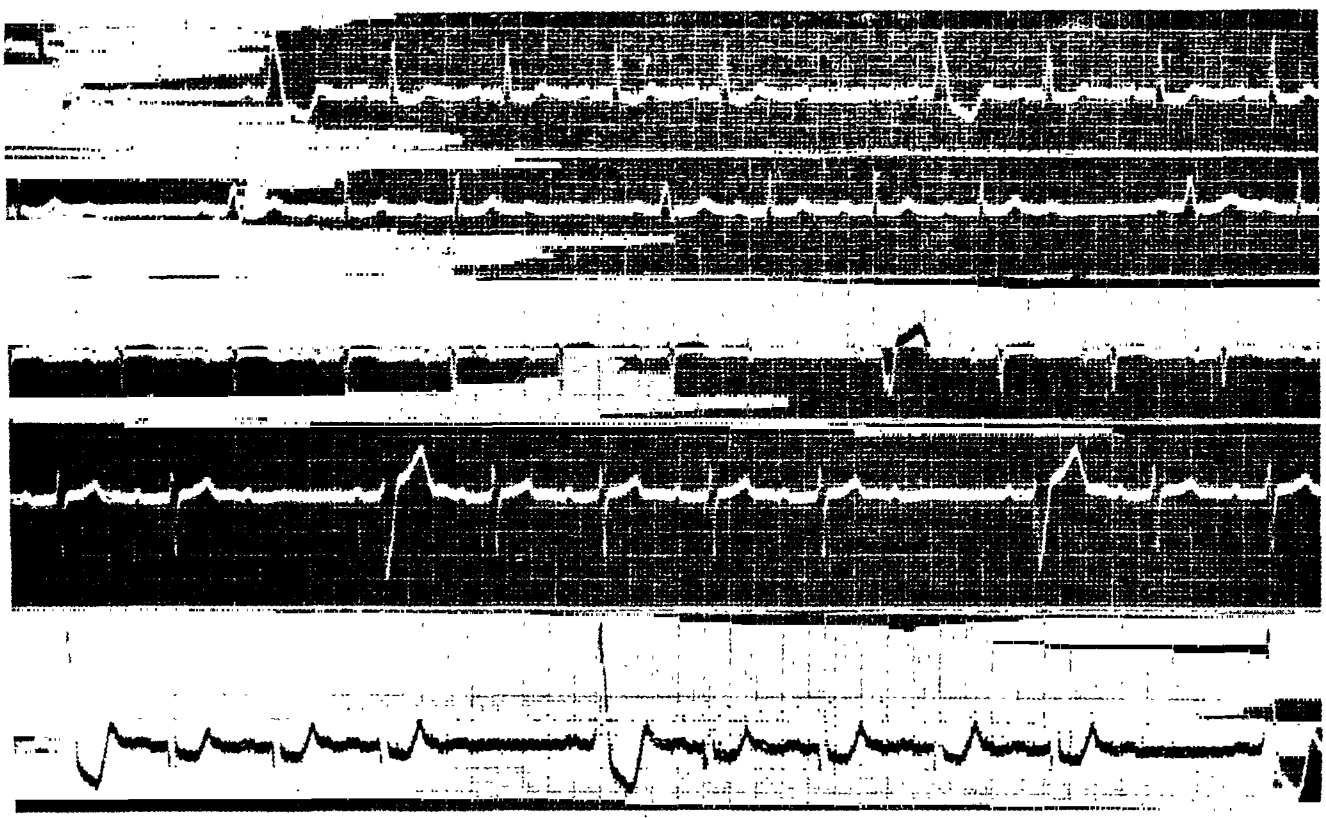

Fig. 2.—Wenckebach's periods and abnormal intraventricular conduction.

monly seen when 2:1 A-V block reverts to a normal sinus rhythm. The RS-T segments show clearly the effect of the digitalis because they are depressed in a characteristic way, particularly in Leads I and CR_4. Unusual, however, is the QRS complex of the first conducted beat after a blocked P wave because it shows the pattern seen during the sinus rhythm and bundle branch block in Fig. 1,*B*. In our opinion, there can be no doubt about the identity of these QRS complexes in the two tracings. The finest slurring and notching are minutely duplicated. Only in the apical chest lead do differences exist, but these are not uncommon because of the fact that in obese patients with a high diaphragm the electrode is very often not placed far enough to the left to be situated over the left ventricle. Note that all complexes, with the exception of the first one after the pause, resemble each other closely.

The P-P, R-R, and P-R intervals in all leads of the tracings from which Fig. 2 was obtained were carefully measured and the data obtained are reproduced in Table I. The auricular rate is seen to vary slightly with a tendency to be slower for one or two cycles following a dropped beat. The R-R intervals during the periods of conduction reveal the same variations as the P-P intervals; the abnormal beats follow the preceding QRS complex after a time which varies between 1.62 and 1.75 seconds. The P-R interval increased markedly from the first to the second conducted beats and increases only slightly just before the dropped beat. The P waves precede the abnormal beats with the fairly constant interval of 0.21 to 0.23 second.

DISCUSSION

The abnormal ventricular complexes appearing in Fig. 2 after the long pause may represent idioventricular beats originating in a ventricular center. This is not a rare phenomenon in tracings with partial A-V heart block. In our opinion, however, the abnormal beats are conducted from the auricle and are not automatic idioventricular beats. This conclusion is based mainly on two facts.

1. The abnormal beats appear to be similar in all details to those observed during the regular sinus rhythm with bundle branch block (Fig. 1,*B*). There is only the slight difference in Lead CR_4 which was discussed. All the details, including notching and slurring of the QRS complexes in the other leads, are the same in the QRS complexes of Fig. 1,*B* and in the abnormal QRS complexes of Fig. 2.

2. The length of the periods before the abnormal complexes in Fig. 2 varies, while the P-R interval of the abnormal beats is fairly constant. If the abnormal QRS complexes were idioventricular beats independent of auricular stimuli, a greater variation of the P-R intervals would be expected.

The conclusion that we are dealing with conducted beats justifies the diagnosis of intermittent bundle branch block. In intermittent bundle branch block with dropped beats, however, the block usually disappears after a longer pause because of the better recovery of the bundle branch involved; if sinus rhythm

TABLE I. AURICULAR AND VENTRICULAR INTERVALS AND AURICULOVENTRICULAR CONDUCTION TIME IN FIVE LEADS

LEAD I			LEAD II			LEAD III			LEAD CR_2			LEAD CR_4		
P-P	R-R	P-R	P-P	R-R	P-R	P-P	R-R	P-R	P-P	R-R	P-R	P-P	R-R	P-R
86	175	22	85	162	32	88	90	26	87	89	27	88	168	30
90	94	26	87	88		88	90	28	87	169	29	88	90	23
86	90	28	83	86	23	88	87	28	86	90	23	86	84	26
88	88	28	84	166	26	86	87	28	85	86	27	85	88	26
86	88	29	85	84	31	88	90	28	86	89	27	86	168	28
85	173	22	86	86	23	84	172	28	86	88	28	84	86	22
88	88	24	82	86	26	92	92	23	88	169	30	92	87	24
92	87	24	86	165	26	88	86	26	88	89	23	84	88	28
84	87	26	82	89	28	88	84	28	88	88	26	86	89	28
84	94	28	84	86	22	82	84	28	88	87	26	86	166	29
88	164	23	88		25	82		28	88	88	27	88	92	22
82	85	24	83		27				87	87	27	84	88	25
84	86	26	84						88		27	90	88	26
86	170	21										88	174	30
84	88	26										86	88	22
84	86	26										86	89	24
80												88		26
92												88		
84												86		
88												88		

Figures represent sec. 100.

without irregularity prevails, bundle branch block appears quite irregularly. In Fig. 2 we find the paradoxic phenomenon of bundle branch block appearing only after the longer pause.

For the explanation of this finding, the supernormal phase of excitation seems to be the most logical. The first impulse arriving at a damaged area of the left bundle branch is unable to traverse it in time to activate the left ventricle directly. An impulse reaches the left ventricle later by way of the septum and over muscular pathways from the right ventricle. This impulse leaves the damaged area in a hyperexcitable state, and if the next stimulus arrives during this state of supernormal excitability, the conduction is so much improved that normal ventricular complexes appear.

The question arises as to whether the supernormal phase can last long enough after every beat to explain the normal conduction of the series of ventricular complexes following the abnormal one. We know that the excitation wave reaches the auriculoventricular node 0.04 to 0.05 second after the beginning of the P wave and is conducted in the bundle branches about 0.05 to 0.06 second later. Therefore, the distance from the beginning of the abnormal QRS complex to the beginning of the following P wave will indicate approximately the moment of conduction in the bundle branch. This time measures in Fig. 2 (Lead I) in the successive cycles: 0.68, 0.62, 0.64, 0.60, 0.64, 0.64, 0.60, 0.59, 0.60, 0.60, 0.60, 0.60 second; that is, it varies between 0.59 and 0.68 second. In Table II is compiled the duration of the supernormal phase after the transmission of an impulse in nerve, in the turtle heart and in the human heart, as reported in the literature. In investigations of the supernormal phase in auriculoventricular block, the duration of the former is usually measured from the beginning of the R wave

TABLE II. DURATION OF SUPERNORMAL PHASE

AUTHORS	DURATION OF SUPERNORMAL PHASE FOLLOWING PRECEDING SYSTOLE (SEC.)	OBJECT
Adrian and Lucas[2]	0.01–0.04	nerve fiber
Ashman[3]	3.00–4.00	turtle heart
Ashman and Herrmann[4]	0.31–0.795 0.09–0.30	human heart human heart
Lewis and Masters[8]	0.425–0.708	human heart
Wolferth[12]	0.45–0.74	human heart
Scherf and Schott[11]	0.10–0.16 0.22–0.28	human heart human heart
Kline and associates[7]	0.6–1.04	human heart
Luten and Pope[9]	0.59–0.64	human heart
Jervell[6]	0.50–0.55	human heart

to the following P wave of an abnormally well-conducted impulse. The table shows that some of the figures obtained in nine different human hearts are well within the range found in our patient.

A case showing many similarities to that described in this paper has been reported previously.[5] The patient was a 19-year-old man who had a history of two attacks of rheumatic fever, and who was admitted during the active phase of a third attack. He had also received digitalis, as had our patient. The electrocardiograms revealed a sinus tachycardia with a rate between 110 and 120 beats per minute. Periodically, dropped beats appeared and the first conducted beat after the blocked P wave showed widening and slurring of the QRS complex similar to that seen in our patient. In discussing the interpretation of this observation Von Hoesslin concluded that the best explanation was an escape of a deep idioventricular center. The same arguments used in our case may be considered valid in rejection of this interpretation. In another interesting case[4] showing features speaking for the existence of a supernormal phase, idioventricular beats appeared which, in the opinion of the authors, originated above the bifurcation of the auriculoventricular conduction system. The longer the rest interval of the preautomatic pause, the wider was the QRS complex of these beats and the slower the intraventricular conduction. The possibility of a supernormal phase, as accepted in our case, was rejected, and the authors believed that the increased intraventricular pressure, following a longer intraventricular block, delays conduction through "pressure block." In our case, this explanation seems improbable since the form of the QRS complexes is constant in spite of variation in the length of the preceding pauses and because of the similarity between the QRS complexes during the bundle branch block (Fig. 1,*B*) and during the abnormal phenomenon. No other forms of the QRS complex were seen in our case but the two shown in Figs. 1 and 2.

The supernormal phase in healthy muscle or nerve tissue is very short and often cannot be demonstrated. It is more readily demonstrable and is markedly prolonged if some tissue damage is present. There is no doubt that myocardial damage existed in the case discussed in this paper. It is difficult to ascertain the nature of this damage. The elevation of the systolic and diastolic blood pressure and the enlargement of the left ventricle in a 56-year-old patient with obesity and mild diabetes make myocardial damage due to coronary sclerosis possible. The evidence of acute polyarthritis with an increased sedimentation rate, leucocytosis, and fever suggests the possibility of myocardial damage caused by an active rheumatic carditis. The fact that abnormal electrocardiograms appeared during a phase when the clinical signs began to improve does not militate against this diagnosis.

In this case, as well as in the case presented by Von Hoesslin, digitalis had been administered. The role that this drug played in the production of the described phenomenon is uncertain, but it may very well have been partly or entirely responsible.

SUMMARY

A case of abnormal intraventricular conduction is reported, which is interpreted as being due to the phenomenon of a supernormal phase of conductivity.

Our thanks are due to Dr. Milton J. Raisbeck for the permission to publish the electrocardiographic tracings.

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Abstracts and Reviews

Selected Abstracts

Mussafia, A.: Electrocardiographic and Clinical Studies on Certain Types of Myocardial Infarction: Supra-apical, Endocardial, Epicardial, Lateral and Anterolateral Infarction. Arch. d. mal. du coeur. 40:369 (Sept.), 1947.

The article presents a classification of myocardial infarcts after a study of 200 instances of infarction observed over a ten-year period. The results were based on standard leads and chest Leads CR_2, IVR, and occasionally on Leads CR_5 and CR_6. Anteroapical infarcts were observed in forty-five cases (22.5 per cent) and posterobasal infarcts in forty-six examples (23 per cent). Supra-apical infarcts (the anteroseptal infarct of Wilson) were present twenty-seven times (13.5 per cent), endocardial infarcts seven times (3.5 per cent), epicardial infarcts nine times (4.5 per cent), lateral infarcts (Type $Q_1T_1CR_5$) five times (2.5 per cent), and anterolateral infarcts (Type $Q_1T_1CR_4CR_5$) four times (2 per cent). "Atypical" infarcts (not discussed) were noted in fifty-seven instances (28.5 per cent). Pathologic confirmation of the electrocardiographic pattern was obtained in twelve cases.

HECHT.

Biorck, G.: Ergotamine and Apparent Coronary Insufficiency. Brit. Heart J. 9:181 (Oct.), 1947.

The author believes that the Levy hypoxemia test not only discloses latent coronary artery disease but that it also produces apparently pathologic electrocardiograms in patients with symptoms of cardiac neurosis in the absence of organic changes in the coronary circulation.

This impression led the author to try to counteract nervous factors which may be present. Blocking of the sympathetic nerves was regarded as one possible way of studying the problem of the importance of functional factors in some cases of unexpected positive hypoxemia tests. Ten neurotic patients without evidence of organic heart disease were studied. The hypoxemia test was performed with 9 per cent oxygen in nitrogen for ten minutes and evaluated according to the criteria of Levy. A few days to one month later, the ergotamine-hypoxemia test was performed as follows: After a previous electrocardiogram taken at rest, the patient was given ergotamine 0.5 mg. intramuscularly or subcutaneously. After twenty minutes an electrocardiogram was taken again. The hypoxemia test was then started. After ten minutes a third electrocardiogram was taken and the patient was permitted to inhale 100 per cent oxygen. Nine of ten positive hypoxemia tests became negative after the administration of ergotamine. This indicates that some factors which contribute to positive hypoxemia tests can be abolished by ergotamine. Further investigations are needed to elucidate this and other mechanisms responsible for positive hypoxemia tests.

SOLOFF.

Parkinson, J., and Papp, C.: Repetitive Paroxysmal Tachycardia. Brit. Heart J. 9:241 (Oct.), 1947.

Repetitive paroxysmal tachycardia is defined as recurring short runs of auricular, nodal, or ventricular extrasystoles. Such runs or paroxysms of tachycardia are almost constantly present for months or for years and only occasionally are interrupted by periods of normal sinus rhythm.

The authors have collected forty cases. The ages of the patients varied from 4 to 75 years. The auricular form was more common in patients under 40 years. Auricular flutter and fibrillation were more common in adults. The longest paroxysmal state was ten years.

The symptoms consisted of: (1) palpitation, independent of exertion, (2) occasional breathlessness, and (3) in six, syncopal attacks. Organic heart disease was present in three patients only.

The electrocardiographic features consisted of: (1) repetitive auricular paroxysmal tachycardia, twenty-four cases; (2) repetitive auricular flutter, four cases and repetitive auricular fibrillation, one case; (3) repetitive nodal tachycardia, two cases; and (4) repetitive ventricular tachycardia, nine cases.

The nature of this condition is unknown. It appears to be a connecting link between extrasystoles and ordinary paroxysmal tachycardia. It may be the result of a congenital peculiarity in the conducting system. The prognosis is good; children tend to grow out of it in adolescence. In adults also it tends to subside. Treatment is usually of no value. Quinidine may be tried but is usually ineffective.

SOLOFF.

Cossio, P., Dambrosi, R. G., and Warnford-Thomson, H. F.: The First Heart Sound in Auricular and Ventricular Extrasystoles. Brit. Heart J. 9:275 (Oct.), 1947.

This study deals with the causes for the variation in intensity of the first sound of a premature beat. Thirty patients with extrasystoles were studied by means of simultaneous electrocardiographic and phonocardiographic records. Sixteen patients had auricular and fourteen, ventricular extrasystoles.

Auricular Extrasystoles.—In all but one subject, the extrasystolic first sound was louder than the first sound of the preceding and the following normal beats. The interval between the onset of QRS and the reinforced first sound varied from 0.05 to 0.08 second, while in the normal beats or premature beats without reinforcement of the first sound, it was 0.03 to 0.05 second. The greatest intensity and delay of the first heart sound occurred when the extrasystolic ventricular systole was in mid-diastole, whereas the less intense sounds occurred when the extrasystolic ventricular systole was in early or very late diastole.

Ventricular Extrasystoles.—The extrasystolic first sound was louder than the normal first sound in nine, of equal intensity in one, of equal or less intensity in one, and of less intensity in three. The interval between the onset of QRS and the increased ventricular extrasystolic first sound was from 0.08 to 0.12 second, while in normal beats it was 0.03 to 0.06 second. Diminished extrasystolic first sounds occurred whenever the premature ventricular systole coincided with the descending limb of the T wave of the preceding cycle or fell just in front of the next P wave of sinus origin. Increased extrasystolic first sounds occurred whenever the premature ventricular systole fell just after the T wave or just after the normal P wave. In four of fourteen cases a split first sound was recorded in the premature beats.

The authors suggest the following explanation for these findings: Normally, the onset of a normal ventricular contraction finds the A-V valves in the position of almost complete closure. With premature contraction, the A-V valves are at a lower position; more time must elapse before their closure, and their movement and, consequently, their vibration is increased. When the onset of premature ventricular extrasystole coincides with auricular systole of sinus origin or when a premature systole falls at the end of or immediately after the phase of rapid inflow, the first sound is intensified and delayed; when it falls before the end of the phase rapid inflow, because of incomplete ventricular filling, the valves are insufficiently stretched to intensify the first sound. The asynchronous contraction of the ventricles in premature ventricular contraction is the cause for the splitting of the first sound. The asynchronous closure of mitral and tricuspid valves also explains why ventricular extrasystoles have a lower incidence of intensified first sound than auricular extrasystoles.

SOLOFF.

Benn, J.: The Prognosis of Patent Ductus Arteriosus. Brit. Heart J. 9:283 (Oct.), 1947.

Benn states that it is important to assess the increased risk that the presence of a patent ductus involves because surgical intervention to correct it is becoming so frequent that some surgeons recommend operation in all uncomplicated cases between the ages of 7 and 10 years. Previous studies on the prognosis are unsatisfactory because no distinction is made between those who had symptoms and those who did not.

Forty-six cases were collected and divided into two groups. Group A, consisting of thirty cases, was collected from a school cardiac clinic in Bristol, save for one woman, 23 years of age, who was referred from an antenatal clinic. This group approximates a good sample of the condition since it probably represents almost every type of case observed in the younger people in Bristol. Group B, consisting of sixteen cases, was collected from areas outside Bristol. The patients composing this group were referred often because of symptoms. Group B approximates more nearly the type of case generally reported. The patients of these two groups were followed for a period of eight years.

Six of Group A and two of twelve surviving members of Group B had symptoms such as breathlessness on exertion, fatigue, cyanosis on occasion, and frequent colds. Five of Group B had bacterial endocarditis and only one, who was cured by penicillin, is alive now.

In two cases the classical murmur had disappeared without other evidence that the ductus had closed. Both the murmur and thrill may vanish with increasing age.

Of forty patients with electrocardiographic tracings, one had left axis deviation and one had right axis deviation; the remaining thirty-eight had no axis deviation. Of fifteen with x-ray studies, all had prominent pulmonary arteries. Eight of twenty patients in Group A and seven of ten in Group B were regarded as having pulmonary congestion on the basis of the appearance of the hilar shadows. Fifteen of seventeen of Group A with weights available were below normal weight. This was especially true for female patients. The female subjects were taller than normal.

No patients in Group A died or developed bacterial endocarditis or heart failure. In Group B, four patients died of bacterial endocarditis and one recovered from this disease.

The author believes that the indications for surgery should be (1) bacterial endocarditis, (2) recovered bacterial endocarditis, (3) cardiac embarrassment, and (4) poor physique.

SOLOFF.

Wiggers, C. J., Levy, M. N., and Graham, G.: Regional Intrathoracic Pressures and Their Bearing on Calculation of Effective Venous Pressures. Am. J. Physiol. **151**:1 (Nov.), 1947.

Intrathoracic pressures were recorded by optical capsules from eight different regions around the canine heart. Only minimal quantities of air were introduced into the mechanically created pockets. It was demonstrated that pressure obtained from pockets of the right lower thoracic cavity are little influenced by variations in pressures induced by cardiac movements but are otherwise similar to those derived from regions adjacent to the heart and that they change directionally with them. Pressures obtained from this region may be used in calculating trends of effective venous pressures.

HECHT.

Gregg, D. E., and Shipley, R. E.: Studies of the Venous Drainage of the Heart. Am. J. Physiol. **151**:13 (Nov.), 1947.

Coronary inflow and venous drainage were measured in fifty dogs by open chest experiments employing visual and optical recording rotameters and an orifice meter (Am. J. Physiol. **142**:44, 1944). With this technique it was found that almost all of the coronary sinus flow arose from the left coronary artery, although only about three-fourths of the flow of the left coronary artery drains by this route. Venous blood of the right heart drains through the anterior cardiac veins.

Acute occlusion of the coronary sinus causes congestion of the left heart, elevates the pressure in the sinus and in the great cardiac veins, increases the flow through the anterior cardiac

veins, and causes little if any reduction in coronary venous inflow. This suggests that the anterior cardiac veins may serve as alternate routes of drainage for the left ventricle. A somewhat similar response (rerouting of run-off with unaltered inflow) is obtained when the anterior coronary veins are ligated. If all visible venous channels are ligated, drainage still occurs, suggesting the presence of extensive collateral drainage channels. In experiments where an attempt was made to ligate all but the Thebesian veins, the ventricles became markedly hemorrhagic except for portions of the inner third of the left ventricle and the septum. It was demonstrated, however, at post-mortem examination that a few veins, possibly serving those regions, had remained unoccluded.

Chronic occlusion resulted in sizable anastomoses between the superficial veins of the heart and the extracardiac veins. It appears from these experiments that the Thebesian vessels play only a limited role in coronary drainage.

HECHT.

LeVeen, H. H., and Fishman, W. H.: Combination of Evans Blue With Plasma Protein: Its Significance in Capillary Permeability Studies, Blood Dye Disappearance Curves, and Its Use as a Protein Tag. Am. J. Physiol. 151:26 (Nov.), 1947.

In man, the percentage of disappearance of Evans blue dye from the plasma varies widely over a twenty-four hour period (approximately 50 per cent) and is far in excess of the albumin turnover. When injected in large amounts, dye may appear in the pancreatic juice (one dog). In vitro experiments demonstrate that T-1824 combines with purified albumin, but also, to a lesser extent, with all globulin fractions. Activated resins remove 50 per cent of the dye from an albumin-dye mixture, suggesting that dissociation of the dye-albumin complex may readily occur. Un-ionized dye molecules may occasionally diffuse past capillary membranes and be fixed by tissue protein (staining) or secreted ("trapped") in ionized form. Tissue staining may in part account for the rapid early disappearance phase upon injection of dye into the blood stream. The rapid turnover of T-1824 and the ready dissociation of the dye-protein complex precludes the use of Evans blue as a tag for protein in metabolic studies.

HECHT.

Root, W. S., Walcott, W. W., and Gregerson, M. I.: Effects of Muscle Trauma and of Hemorrhage Upon the Cardiac Output of the Dog. Am. J. Physiol. 151:34 (Nov.), 1947.

Shock ensues when the blood volume of dogs is reduced by 30 to 40 per cent following muscle trauma. The cardiac output in fourteen dogs, as determined by the Fick method, was found to be reduced to only 10 to 25 per cent of the control values, with exceedingly small outputs per beat (1 to 3 ml.). Calculated peripheral resistance increased one- to fivefold over the control values. The changes are less pronounced in dogs that did not develop shock following the trauma. Similarly, cardiac output decreased immediately following hemorrhage in twelve dogs bled 10 to 50 per cent of their control blood volumes. In this group, blood pressure changes were more pronounced and increases in peripheral resistance less striking than in the traumatized animals.

HECHT.

Miller, A. T.: Excretion of the Blue Dye, T-1824, in the Bile. Am. J. Physiol. 151:229 (Nov.), 1947.

Ligating the cystic duct of nine dogs allowed the collection of hepatic bile before, during, and following the administration of Evans blue. Dye appeared in the bile thirty minutes after injection into the blood stream and reached a maximum concentration within the second hour. Bile accounted for only 2 to 7 per cent of the dye leaving the blood stream during that interval. The dye concentration in the bile appears to be independent of bile flow and is usually less than one-half the plasma dye concentration.

HECHT.

Miller, A. T.: A Re-evaluation of the T-1824 Mixing Curve. Am. J. Physiol. 151:234 (Nov.), 1947.

The true disappearance slope of the Evans blue dye from plasma is preceded by mixing of the dye in the plasma. This may be divided into a rapid phase (Phase I), interpreted as demonstrating mixing of freely circulating plasma, and into a slower phase (Phase II) reflecting diffusion of dye into noncirculating plasma. In dogs, the first phase appears to be completed in four to six minutes, the second in thirty to fifty minutes. Extrapolation of Phase II of the mixing curve permits calculation of circulating plasma, while extrapolation of the true disappearance curve provides an index of total plasma volume. In 105 experiments on twenty-four dogs, the average circulating plasma volume was 86 per cent of the total plasma volume.

Cruickshank and Whitfield's conclusions that the extrapolation of Phase I of the mixing curve represents the true plasma volume are again challenged.

HECHT.

White, H. L., Heinbecker, P., and Rolf, D.: Endocrine Influences on Cardiac Output and Oxygen Consumption in Dogs. Am. J. Physiol. 151:239 (Dec.), 1947.

Thyroidectomy and hypophysectomy produce prompt and permanent falls in oxygen consumption and in cardiac output in normal dogs as measured by the Fick principle. Administration of anterior pituitary hormone (Preloban) increases oxygen consumption and restores cardiac output in the hypophysectomized animal and also, to some extent, in the thyroidectomized animal. Preloban increases cardiac output in the normal dog. Denervation of the neurohypophysis does not alter cardiac output and oxygen consumption. These findings parallel *previously observed changes in renal blood flow produced by the same procedures. It is postulated* that the anterior lobe of the pituitary gland produces a substance which brings about increase in oxygen consumption, in cardiac output, and in renal flow. The observed effects cannot be explained by the action of thyrotropic or adrenocorticotropic hormones.

HECHT.

Lawson, H. C., Overbey, D. T., Moore, J. C., and Shadle, O. W.: Mixing of Cells, Plasma and Dye T-1824 in the Cardiovascular System of Barbitalized Dogs. Am. J. Physiol. 151:282 (Dec.), 1947.

The circulatory mixing of cells, plasma, and dye solutions was studied in barbitalized and splenectomized dogs. It appears that complete mixing is accomplished in from three to five minutes when mixing times are determined by arterial hematocrit determinations and optical densities of dyed plasma. Continued rapid disappearance of injected dye beyond the first five minutes is ascribed to escape of dye from the vascular compartment.

HECHT.

Overbey, D. T., Moore, J. C., Shadle, O. W. and Lawson, H. C.: Rate of Disappearance of Dye T-1824 From Arterial Blood. Am. J. Physiol. 151:290 (Dec.), 1947.

Full logarithmic plotting of dye disappearance curves demonstrates a relationship between dye concentration and time that is expressed $C_t = \frac{C_1}{T^p}$ where C is the dye concentration at time t, C_1 is the concentration at one minute; T, the time of injection in minutes; and p, a fractional power (0.0554). A truly exponential rate of dye disappearance is achieved only after two to four hours and three phases of dye disappearance are recognized: an initial rapid disappearance phase (one hour), an intermediate phase (one to three hours), and finally after three hours, a truly exponential phase. Any injection of dye into a previously dye-injected animal must pass through all three phases. A first and a second injection of dye behave identically when allowance is made for the changing rate of disappearance in time. (This is at variance with the reports of Cruickshank and Whitfield.)

HECHT.

Grollman, A.: Effect of Pregnancy on the Course of Experimental Hypertension. Am. J. Physiol. 151:373 (Dec.), 1947.

Hypertension was induced in rats, rabbits, and dogs by application of a constricting figure-of-eight band to both kidneys or to one kidney with removal of the other. A tendency for the blood pressure to decline during pregnancy was noted in all experiments. The response decreased with increasing size of the species. Pseudopregnancy, induced in the rat by stimulation of the cervix and in the rabbit by mating with sterile partners, and occurring spontaneously in dogs following estrus, did not alter the blood pressure of the hypertensive animals. The reduction in blood pressure is considered to be primarily the result of the increased size of the vascular bed induced by the presence of the placenta. There were no symptoms suggestive of eclampsia and there was no tendency to abortion or fetal death among the hypertensive animals.

HECHT.

Morse, M., Cassels, D. E. and Schlutz, F. W.: Available and Interstitial Fluid Volumes of Normal Children. Am. J. Physiol. 151:438 (Dec.), 1947.

Simultaneous determinations of plasma volume and thiocyanate space, following the method of Gregerson and Stewart, were performed on sixty-five children varying in age from 3 to 17 years. The data are correlated statistically for age, height, weight, surface area, height and weight, height and index of build, height and chest girth, and weight and index of weight. The average available fluid volume measured 287 ml. per kilogram of body weight. Surface area was found to be the best standard of reference. The fluid volume did not vary with the state of nutrition and remained relatively constant throughout the age range studied when related to unit of body weight. From available data it appears that the available fluid volume for the child and adolescent exceeds that of the adult when expressed in milliliters per kilogram of body weight.

HECHT.

Nichol, A. D. and Brannan, D. D.: The Differentiation of Patent Ductus Arteriosus and Atrial Septal Defect. Am. J. Roentgenol. 58:697 (Dec.), 1947.

In patent ductus arteriosus, blood from the aorta is shunted into the pulmonary artery. The artery dilates to accommodate the increased blood volume, which on returning to heart results in enlargement of the left atrium. The increased filling of the left atrium and left ventricle increases the systolic output delivered to the aorta. Roentgenographically, these facts are manifest by the unusual combination of slight left atrial enlargement, definite left ventricular enlargement, and definite enlargement of the pulmonary artery and the first and second portions of the aorta. Clinically, there is usually no cyanosis, usually typical murmurs, localized pulsations in the second left intercostal space, a high systolic and low diastolic blood pressure, a normal electrocardiogram or left axis deviation, and slight circulatory insufficiency.

In atrial septal defect, the right atrium receives the peripheral venous flow and in numerous instances, a large complement of blood from the left atrium. This increased volume of blood causes enlargement of the right atrium and right ventricle; it also increases the right ventricular systolic output which results in considerable enlargement of the entire pulmonary vascular system. When this increased blood volume is returned to the left side of the heart, the septal defect shunts part of the blood from the left to the right atrium. This prevents an otherwise extreme enlargement of the left atrium and also results in decreased left ventricular filling, which, in turn, results in decreased left ventricular output and decreased peripheral blood flow. These changes are manifest roentgenographically by an increase in heart size due to marked increase in the size of the right atrium and right ventricle, associated with dilatation of the pulmonary artery and its branches. In contrast, the aortic knob is small and inconspicuous. Clinically, there is a variability of murmurs and thrills; right axis deviation and abnormal P waves in the electrocardiogram, which may also show an unstable cardiac conduction mechanism; minimal transient cyanosis; subnormal physique; low systolic blood pressure and narrow pulse pressure; and localized prominence of the left anterior chest wall in the region of the second, third, and fourth intercostal spaces.

The authors believe that uncomplicated cases of these two common congenital abnormalities can be diagnosed in a large percentage of the cases by observation of the features presented.

ZION.

Freeman, N. E., Leeds, F. H., and Gardner, R. E.: Sympathectomy for Obliterative Arterial Disease; Indications and Contraindications. Ann. Surg. 126:873 (Dec.), 1947.

In the management of obliterative arterial disease of the extremities, sympathectomy has two functions: first, the abolishment of vasomotor tone and, second, the abetment of the collateral circulation. The authors point out that the greater the evidence of overactivity of the sympathetic nervous system, the better the results following sympathectomy. There are six guiding points which indicate an increase in vasomotor activity in an extremity: (1) coolness; (2) sweating, the combination making for a "cold, clammy foot or hand"; (3) cyanotic mottling of the digits; (4) constriction of the superficial veins; (5) delayed blanching of the extremity on elevation; and (6) the patient's subjective statement of improvement in the extremity following a paravertebral novocaine block.

In patients with obliterative arterial disease, whether it be due to thromboangiitis obliterans or to arteriosclerosis, if evidence of a high degree of vasomotor tone is present, then sympathectomy is indicated. Conversely, if little or no evidence of vasomotor activity is present, sympathectomy is not only useless but may actually prove to be harmful.

The authors cite Atlas' signs which contraindicate sympathectomy: (1) severe extensive arterial occlusion; (2) rapid blanching on elevation of the extremity; and (3) atrophy of skin and subcutaneous tissues. In addition to three cases reported by Atlas, the authors report four patients who were made worse by sympathectomy. All had evidence of low vascular tone and should not have been subjected to the operation.

The explanation of these observations lies in the fact that there is a dual anatomic structure in the peripheral circulation. First, there is the arteriovenous anastomosis in the form of the neuromyoarterial glomus, and second, the nutrient capillaries. The former is under the control of the sympathetic nervous system and is important in conservation and release of heat as well as serving as important shunts between the arterial and venous systems. When there is extensive arterial obliterative disease, sympathectomy opens these glomus shunts and indirectly interferes with the circulation through the capillaries, with consequent gangrene of an extremity in some cases.

LORD.

Cabrera, E., and Sodi-Pallares, D.: Discussion of the Circus Movement. Proof of Its Occurrence in the Clinical Auricular Flutter. Arch. inst. cardiol. de Mexico 17:850 (Dec.), 1947.

The authors have studied the characteristics and possible modifications of the circus movement in clinical auricular flutter. The following conclusions were reached:

1. Rotation of the instantaneous axis is not in favor of a circus movement in auricular flutter; it is only evidence of the curve described by the vectocardiogram of the flutter which is also present in other cyclic electrical phenomena.
2. Intravenous injection of acetylcholine causes the acceleration of both the auricular and the ventricular rates. This can be used in the differential diagnosis between auricular flutter and auricular tachycardia because in the latter, acetylcholine either ends the attack or has no effect.
3. Intravenous injection of a large dose of acetylcholine in cases of flutter has never caused an auricular rate similar to that observed in auricular fibrillation, and no irregularity of the auricular waves was observed.
4. The acceleration of flutter caused by acetylcholine supports the theory of a circus movement.
5. The time of activation of the auricles was further studied by simultaneous tracings of esophageal and precordial leads. While the ventral aspect of the auricular mass was activated from above downward, the dorsal aspect was activated from below upward. This is in favor of the existence of a circus movement.

6. Rotation of the instantaneous axis and the auricular vectocardiogram suggested in all cases of flutter, except one, that the wave of activation was descending in the anterior part and ascending in the posterior part of the ventricular mass.

7. The rotation plane of the auricular vectocardiogram was further found in agreement with the hypothesis of a circus movement around the orifices of both venae cavae.

LUISADA.

Alzamora Castro, V.: Contribution to the Study of S-T Changes, Angina Pectoris and Subendocardic Infarctions. Arch. inst. cardiol. de Mexico 17:870 (Dec.), 1947.

The authors describe in detail the anatomic, clinical, and electrocardiographic characteristics of a case with extensive subendocardial infarction involving the entire left ventricle and part of the right ventricle. The patient had repeated and almost continuous attacks of precordial pain during which the electrocardiogram showed downward displacement of the S-T interval in leads where the exploring electrode was near the epicardial surface, and upward displacement in those leads which record the cavity potentials.

A clinical diagnosis of a subendocardial infarction was made. At necropsy the subendocardial necrosis was found to be secondary to partial obliteration of the orifices of both coronary arteries caused by syphilitic aortitis. It is not known why a total decrease of the coronary blood flow should cause a selective subendocardial damage. A hypothetical explanation, based on mechanical factors, is advanced by the authors. The electrocardiographic changes encountered during the attacks of angina pectoris are similar to those reported in the present case. During the pain, a metabolic disturbance, probably related to oxygen deficiency, seems to occur; this affects chiefly the deeper or subendocardial portions of the left ventricle and is accompanied by electrical forces which produce transient electrocardiographic changes. When the circulatory disturbance is severe, prolonged, or repeated, as in this patient, the alterations may reach the stage of necrosis (infarct).

Certain clinical syndromes simulating coronary occlusion present electrocardiographic changes similar to those recorded during the attacks of angina pectoris and are probably due to the same basic circulatory changes. These cases have been classified by the authors as "subendocardial infarcts" and are characterized electrocardiographically by more or less permanent modifications of the S-T interval.

LUISADA.

Hejtmancik, M. R., and Herrmann, G. R.: Paroxysmal Ventricular Tachycardia With Special Reference to Treatment. Texas State J. Med. 53:505 (Dec.), 1947.

A series of twenty cases of paroxysmal ventricular tachycardia has been analyzed by the authors. The average age of the patients in the series was 52.8 years, the youngest being 18 and the oldest, 80 years of age. Coronary artery disease was present in 70 per cent of the cases. The rates of the tachycardia varied between 110 and 220, with an average of 170 per minute. No correlation was observed between heart rate and prognosis. Fifteen of the cases were associated with signs of congestive failure. Three patients showed cerebral manifestations; in two these were due to the tachycardia itself, and in one they were secondary to cerebral embolism. One of these had generalized convulsive seizures and another had attacks of syncope. Of two patients with apparently normal hearts, one complained of precordial burning and the other had no symptoms referable to the disorder.

In three of the four patients receiving no specific therapy, the disorder persisted until death. Ten of twelve cases reverted to a normal rhythm on quinidine, given orally; the amount required varied from 0.6 Gm. to 5.2 Gm. in twenty-four hours. In one patient with acute myocardial infarction, the rhythm was not abolished by 11.8 Gm. of quinidine, given orally, over a period of four days, and the patient died. The two patients with no demonstrable heart disease were successfully treated, one with small and one with large oral doses of quinidine. In one patient, whose tachycardia reverted to a normal rhythm with intravenous injection of 16 mg. of morphine, even small doses of quinidine were found to prolong the QRS complex more than 25 per cent.

After reversion of the tachycardia to a normal rhythm, twelve patients were maintained on quinidine sulfate, orally, in doses of from 0.6 to 1.0 Gm. daily. In ten cases paroxysmal ventricular tachycardia did not recur on this maintenance regime. However, four of these patients died within one week, in spite of the established and maintained normal rhythm.

Two patients, in critical condition following myocardial infarction, were given quinidine intravenously. One had not responded to intravenous dosages of morphine of 11, 11, and 32 mg., and oral quinidine totalling 2, 5, and 3.3 Gm. on three successive days. This patient reverted to normal rhythm after 1.7 Gm. of quinidine sulfate was given by slow intravenous drip. Another patient, who was admitted in shock, showed no change in rhythm after being given 0.6 Gm. of quinidine sulfate intravenously in 10 c.c. of distilled water and died in about one hour. One patient under treatment for subacute bacterial endocarditis was given 1.0 Gm. of quinidine sulfate intravenously in divided doses over a period of twelve hours, and then reverted to normal rhythm after 1.2 mg. of Cedilanid was administered intravenously. The intravenous injection of 16 mg. of morphine sulfate resulted in immediate cessation of the abnormal rhythm in one patient with myocardial infarction. In another patient, the ventricular tachycardia reverted to sinus rhythm on carotid sinus pressure six minutes after 45 mg. of morphine sulfate had been given intravenously, the disturbance having been unaffected previously by repeated carotid sinus stimulation and 32 mg. of morphine.

BELLET.

American Heart Association, Inc.

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1949 CAMPAIGN IN PLANNING STAGE

Planning and organizational work on the Association's 1949 campaign has been started, under the active leadership of the new Chairman of the Board, A. W. Robertson, Chairman of the Westinghouse Electric Corporation. National Heart Week, which will be observed February 14 to 21, will highlight the educational and fund-raising drive.

Thomas I. Parkinson, President of the Equitable Life Assurance Society of America, has been named Chairman of the National Sponsors Committee, which will be composed of prominent leaders in all fields of endeavor. This committee will lend prestige to the campaign and inspire the widest public support.

A National Campaign Planning Committee also is being organized among influential and outstanding citizens who will be delegated with responsibility for the conduct of the campaign. They will be directed by a National Campaign Chairman, still to be selected.

Other national committees covering various fields of activity are being formed under the direction of E. J. Ade, who has been appointed Fund-Raising Director for the Association. Mr. Ade formerly was associated with the John Price Jones Corporation as technical director for many major war funds drives, including British War Relief, the Red Cross, USO, and War Bonds. The committees now in formation will include representatives of medical groups, corporations, foundations, women's organizations, labor unions, clubs, and the publicity, sports, and entertainment fields.

A field staff is being briefed to assist local affiliates in their organizational as well as fund-raising efforts. One of the major objectives during the coming year will be the formation of additional local heart associations.

As in the previous campaign, cooperation of national service groups, clubs, fraternal organizations, and trade associations will be sought in the development of local campaigns.

All local efforts will be supported by a nationwide program of radio, newspaper, and magazine publicity which is now being planned. New educational pamphlets and posters are being designed, and preparation is being made for wide distribution of the Plastic Heart collection bank.

MONSANTO AIDS PLASTIC HEART PRODUCTION

The Monsanto Chemical Company has made an important contribution to the heart campaign by making a substantial reduction in the price of the Lustron plastic material which will be used in manufacturing the Plastic Heart collection banks. This will greatly reduce the unit cost of the Plastic Hearts, which have proved an extremely valuable device for canvassing as well as for collections in retail stores and other locations.

FIRST RESEARCH GRANT

The Association has made its first research grant, presenting $25,000 to the Szent Gyorgyi Research Foundation, Inc. The grant will aid studies in muscular contraction being conducted by Dr. Albert Szent Gyorgyi, Research Director of the Foundation, and his associates, at the Marine Biological Institute, Woods Hole, Mass.

The grant is the first in a series which the Association is undertaking as a result of this year's initial nationwide fund-raising campaign.

Dr. Szent Gyorgyi is a winner of the Nobel Prize in Physiology and Medicine. He came to the United States from Hungary in 1946 at the invitation of the Massachusetts Institute of Technology.

POLICIES TOWARD AFFILIATES IN NEW BOOKLET

Policies recently adopted by the Assembly of the Association indicating the nature of relationships with local affiliates have just been issued in booklet form. They are available on request to the Association. The policies cover standards for affiliation of local heart associations, financial relationships, organizational structure, research, relations with other voluntary agencies, and division of principal responsibilities between the national Association and its affiliates.

NATIONAL ADVISORY HEART COUNCIL

The new National Advisory Heart Council, authorized by the bill creating a National Heart Institute in the United States Public Health Service, held its inaugural meeting in Washington September 8. Medical members of the Council include C. A. Elvehjem, Ph.D., University of Wisconsin; Dr. Tinsley R. Harrison, Southwestern Medical College; Dr. T. Duckett Jones, Helen Hay Whitney Foundation; Dr. Irvine Page, Cleveland Clinic; Dr. B. O. Raulston, University of Southern California School of Medicine; and Dr. Paul D. White, Massachusetts General Hospital. Lay members include James S. Adams, businessman, New York; Maurice Goldblatt, merchant and philanthropist, Chicago; Mrs. Albert D. Lasker, leader in public health affairs, New York; E. B. MacNaughton, publisher, Portland, Ore.; Ernest Mahler, Wisconsin businessman; and Albert J. Wolfe, President of the Board, Touro Infirmary, New Orleans.

The Council is authorized to carry out the following specific functions:

A. To review research projects in the cardiovascular diseases, applications for grants-in-aid for heart disease research projects, and applications for grants for training, instruction, and traineeships in the heart field; and to certify approval to the Surgeon General of those projects or applications which it believes will make significant contributions to human knowledge of diseases of the heart or will best carry out the purposes of the Act.

B. To collect information on studies being carried on in this country or abroad on diseases of the heart and, with the approval of the Surgeon General, make this information available to physicians, scientists, public and private health and welfare organizations, and the general public.

C. To recommend to the Surgeon General acceptance of conditional gifts.

D. To advise, consult with, and make recommendations to the Surgeon General with respect to carrying out the Act's provisions.

REGISTRY OF CARDIOVASCULAR DISEASES

The American Heart Association has appropriated $2,500 toward the establishment of a Registry of Cardiovascular Diseases as a unit of the American Registry of Pathology, which is under the auspices of the National Research Council.

The Registry will be administered by the Scientific Director of the American Registry of Pathology with the assistance of a Committee on the Registry of Cardiovascular Diseases of the Association. The Committee, which is now being formed, will create and supervise the policies of the Registry so as to make it of greatest interest and usefulness to specialists in the subject. One of its first duties will be to advise on the preparation of an appropriate blank for submitting cases to the Registry.

The purpose of the Registry will be to collect and report on data and material from cases of all types of cardiovascular diseases, furnish consultation service, prepare teaching material, and pursue definitive studies.

Material sent to the Registry by physicians, hospitals, or other reliable sources may consist of fresh or fixed pathologic specimens, slides, roentgenograms, electrocardiograms, drawings,

case records, or other data. Fresh specimens should be submitted when possible to permit dissection and orientation, and they should be accompanied by complete relevant data.

All material and correspondence should be sent to the Director, Army Institute of Pathology, 7th Street and Independence Avenue, S. W., Washington 25, D. C.

Material collected will be studied by the staff of the Institute and by pathologists, cardiologists, or other specialists on a consultant basis to the Institute. Correlation between the clinical data available and the findings on pathologic study in the registries should be made by the Institute staff and the consultants. Reports of the clinico-pathologic correlations will be made to the contributors and will be used by the staff in selecting material for inclusion in an atlas on cardiovascular diseases, a loan collection of slides showing all types of cardiovascular diseases collected by the Registry, and in preparation of cases for loan to be used at clinico-pathologic conference.

The contributor does not lose control of registered cases incorporated into the Institute files. He is still privileged to report them independently and may have the assistance of the Institute in preparing his illustrations. Permission of the contributor is obtained before his case is used in a study.

AHA ANNUAL MEETING, JUNE 3-4

The next annual meeting of the Association will take place at the Chalfonte-Haddon Hall, Atlantic City, N. J., on June 3 and 4, 1949. The Scientific Sessions will be held in the Vernon and Garden Rooms which accommodate 1,000 persons. Reservations should be made by writing directly to the hotel, at the earliest possible date, stating the exact type of accommodation desired and definite dates of arrival and departure.

DR. ANTONIO BATTRO DIES

Dr. Antonio Battro, distinguished Argentine cardiologist who made important contributions to medicine, died on May 24. He was well known in the United States. For the past few years, he was chief of the Department of Cardiology of the Institute de Investigaciones Fisicas Aplicadas a la Patologia Humana. Dr. Battro is the author of numerous scientific publications and the winner of many awards. In Argentina, he received the Luis Guemes Prize in 1928 and 1938, and the Premio Nacional de Ciencias in 1930.

DR. ERNSTENE HEADS MEDICAL DEPARTMENT

Dr. A. Carlton Ernestene has been appointed head of the Division of Medicine at the Cleveland Clinic. Dr. Ernstene joined the Clinic Staff in 1932 and has been head of the Section on Cardiovascular Disease for many years. He recently was elected president of the Cleveland Cardiovascular Society.

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Original Communications

THE AMOUNT OF DIGITOXIN (DIGITALINE NATIVELLE) REQUIRED FOR ADEQUATE DIGITALIZATION

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New York, N. Y.

In recent years, digitalis glycosides have been substituted for the whole digitalis leaf in the treatment of circulatory disorders. Although observations on the effects of these drugs are now extensive, important questions concerning their optimal dosage and method of administration have not been finally answered.

Using the effect of the drug on the ventricular rate of auricular fibrillation as a criterion, Gold and his associates have presented charts indicating that digitoxin and the whole leaf are absorbed from the gastrointestinal tract at approximately parallel rates.[1-3] They also have reproduced charts showing that the slowing of ventricular rate is slightly more rapid when digitoxin is given intravenously than when given by mouth, but the optimal effect is observed at approximately the same time in each.[1-4] They reproduced one chart, however, (Patient B. S.[1]) in which the slowing proceeded at approximately the same rate in both routes of administration. One would infer that the effect of the whole leaf, administered by mouth, may be as rapid as that obtained from the use of digitoxin intravenously. The authors believe that digitoxin is more completely absorbed from the gastrointestinal tract than the whole leaf since it takes a larger amount of the whole leaf to induce a comparable effect.[1,2] They state: "When one gives a dose of digitalis by mouth in the form of the leaf or of the tincture, only about one-fifth is absorbed. The remaining four-fifths contributes nothing to the therapeutic action."[2]

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Gold and his co-workers further maintain that 1.0 mg. of digitoxin is equivalent to 1.0 Gm. of powdered leaf.[1,4] They state that the average dose of Digitaline Nativelle for full therapeutic digitalization is 1.2 mg.[1,2,4-6] which may be compared with 1.8 Gm. which we found to be the average digitalizing dose of the whole leaf (New York Heart Association preparation).[6-8] They state that 1.2 mg. is the average full digitalizing dose[5] without qualification, but in other publications indicate that there are some patients who may require more or need less.[1,2] Examination of their data does not reveal clearly the derivation of their average digitalizing dose nor do they make a definite statement of their criteria for full therapeutic digitalization. In a paper[1, p. 188] in which they discuss the use of the slowing of the ventricular rate as a guide to digitalis effect, they do not make a definite statement about what degree of slowing is to be the objective. From the chart[1, Fig. 2] which is a composite of data relating to several patients with varying degrees of slowing by digitoxin, it is not possible to determine how many were adequately digitalized by 1.25 milligrams. Indeed, Gold states: "We have not made a distribution or a scatter curve of the therapeutic effects of the 1.2 mg. given at one time. We have made the scatter curve with the maintenance dose of 0.2 mg. which we have just discussed. We have not done this yet with the single dose digitalization."[6, p. 1680] Again, he says, "While we have not determined precisely what proportion of patients are fully digitalized by the 1.2 mg. dose given at one time, we do have some information about that dose since it produces an effect equal to 1.2 Gm. of digitalis."[6] Gold and his associates state categorically that single dose digitalization with 1.25 mg. of digitoxin is a safe and satisfactory procedure.[1,2,4,5] On the other hand, De Graff[9] finds that this amount digitalized less than 20 per cent of his patients who were being digitalized for the first time. He considers the average digitalizing dose to be 2.2 milligrams. Katz and Wise[10] did not assay the amount of digitoxin required for full digitalization; they state, however, that after 1.2 mg. were given it was necessary sometimes to follow with further smaller doses before adequate digitalization was obtained. They did not give their criteria for digitalization.

With such conflicting statements, one must remain in doubt concerning optimal dosage and indeed may question whether Gold's repetition of the statement that 1.2 mg. is the average full therapeutic digitalizing dose may not be harmful to patients who require more for complete digitalization.

There has also been much discussion as to the equivalence of single and divided doses of digitoxin. In our experience with the digitalis leaf administered orally, it was found that safe and satisfactory digitalization could be obtained with 1.8 Gm. (New York Heart Association preparation) in the average patient either in divided doses[11,12] or, when there was urgency and the strength of the preparation was known, by a single large dose.[13] Translation of this experience to the use of digitoxin has not been satisfactorily demonstrated.

In our studies with digitoxin* we chose patients with auricular fibrillation because the slowing of the ventricular rate is a satisfactory guide to digitalis effect. We attempted to reduce the rapid ventricular rates in auricular fibrilla-

*Digitaline Nativelle was used in this study.

tion in twenty-four hours to around 70 to 75 per minute, which is the rate we consider the optimal one for therapeutic purposes,[8] a matter concerning which there is general agreement.

Levine[14, p.274] states with respect to the use of digitalis in auricular fibrillation, "The hope is to slow the apex rate to 60 or 70 per minute if possible, without producing any ill effects." Further, "If the heart rate has slowed to 70 the dose is reduced to 0.1 Gm. a day." He also states,[14, p.286] "A heart that is beating irregularily at a rate of 60 to 70 can be about as efficient as if it were beating regularily at a rate of 70 to 80. In fact a slow irregular rate may maintain a better circulation than a rapid regular one. It was occasionally found that in the presence of stubborn congestive heart failure when the regular rate was 100 or more, improvement might first become manifest only after auricular fibrillation developed. What would happen was that digitalis that was given failed to slow the regular rhythm and when auricular fibrillation began the drug slowed the ventricular rate to 60 or 70 and congestion began to clear." White[15, pp.770 and 771] points out that slowing the ventricular rate in auricular fibrillation from 160 to 60 per minute "means sparing the heart muscle an unnecessary and often ineffective amount of labor consisting of 6,000 beats an hour or well over 100,000 beats a day. Even a reduction of but 50 beats, which is common, say from a rate of 120 to one of 70, means an omission of 72,000 contractions a day." Gold,[5] in speaking of digitalizing, says, "The decline of the ventricular rate to about 70 per minute is the most satisfactory guide." Gold[3, p.552] also states in discussing the use of digitalis in auricular fibrillation, "The desired effect is to maintain a rate of 70 per minute." Levy[6, p.1677] makes the following statement in discussing maintenance dosage of Digitaline Nativelle: "We have seen patients with auricular fibrillation who could be maintained at the proper rate, and by 'proper rate' I mean one that does not rise above 80 under ordinary exertion with as little as 0.1 mg. every second day."

It has been our experience that the clinical dosage of digitalis required for full therapeutic digitalization can be established on patients with rapid auricular fibrillation. The amount of the drug, which by complete absorption in twenty-four hours will slow the ventricular rate to around 70 to 75 per minute, has been found in our experience to be the optimal therapeutic amount in the clinical use of the drug. This has appeared to be approximately the same for all adult patients, irrespective of body weight. The amount of the preparation which accomplished this is then found to achieve therapeutic digitalization in patients with normal sinus rhythm in whom there is not the guide of heart rate as in patients with auricular fibrillation.[8,11,12] Spreading the amount of the drug to be given for full digitalization over a period of eighteen hours does not increase the amount required for digitalization, because excretion during the first twenty-four hours can be neglected for clinical purposes or at most could only make the difference of one daily maintenance.[11] We are of the opinion that digitalization can and should be accomplished without nausea and vomiting.

Our investigations concerned twenty-six patients and included two phases: (1) The hospital records of all patients from 1942 to 1946 having auricular fibrillation who received digitoxin were reviewed to ascertain the effect of this

drug on ventricular rate, and (2) observations were made on the amount of digitoxin required, according to our standards, to produce full digitalization in patients with auricular fibrillation. Many patients who received the drug were excluded from the analysis for the following reasons: (1) the use of other drugs, (2) the onset of complications, (3) the simultaneous use of digitalis and potassium iodide in hyperthyroid patients, and (4) inadequate control periods.

The following observations on digitoxin were made: (1) The effect of digitoxin, 1.2 mg., given in one intravenous dose, was observed in four patients (Cases 1, 2, 3, and 4). (2) The effect of digitoxin, 1.2 mg., given in one oral dose, was observed in four patients (Cases 5, 6, 7, and 8). (3) The effect of digitoxin, 1.2 mg., as the initial dose, followed by supplementary amounts to complete digitalization, was observed in six patients (Cases 3, 4, 5, 6, 7, and 8). (4) The effect of digitoxin, 1.8 mg., in a single oral dose, was recorded in four patients (Cases 9, 10, 11, and 12). (5) The effect of digitoxin, 1.8 mg., as the initial dose, followed by supplementary amounts to complete digitalization, was observed in two patients (Cases 11 and 12). (6) The effect of digitalization with digitoxin in smaller or divided amounts was observed in ten patients (Cases 13, 14, 15, 16, 17, 18, 19, 20, 21, and 22). (7) Observation was made of amounts of digitoxin to achieve digitalization in four patients (Cases 23, 24, 25, and 26) with hyperthyroidism. (8) An attempt was made to ascertain the maintenance dosage of digitoxin. (9) An attempt was made to discover if comparable digitalization occurred when the equal doses of the drug were given orally and intravenously.

In patients in whom the amount given in one dose or in divided doses during the first day was inadequate to reduce the ventricular rate to 70 to 75 per minute, and to whom additional amounts were given on subsequent days to achieve satisfactory digitalization, we have calculated the digitalizing amount, if all had been given on the first day, in the following manner. Experience with the whole leaf has shown that during the first day and with equal total amounts of drug the degree of digitalization is essentially the same with single or with broken dosage. For practical purposes excretion on this day can be neglected. After satisfactory digitalization was attained we tried to assay the maintenance amount in the patient to keep the ventricular rate at the level of 70 to 75 per minute. From the total amount necessary to achieve digitalization and also maintenance over x days is subtracted the maintenance requirement over $x - 1$ day, to give the amount which should have been given on the first day to secure the required level of digitalization for that patient; this is called the calculated digitalization dose for the patient. We have reason to believe that this is valid for the following reasons: (1) The amount corresponds closely with the amount which was required when given in twenty-four hours. (2) We have found that in the digitalization of ambulatory patients with the whole leaf we can attain digitalization in a selected and allotted time if we give over that period the digitalizing amount (1.8 Gm.), plus the total maintenance amount to take care of excretion.[8] We are aware that a patient can be digitalized over a long period by being given small amounts daily, a certain amount of this being retained toward digitalization.

PROCEDURE

On admission to the hospital, the patients were observed during a preliminary control period of two or more days of complete bed rest on a low-salt diet. The fluid intake was fixed, the amount depending on whether or not cardiac failure was present. Daily observations were made on the cardiac and general clinical status of the patient. Apical and radial rates were counted every four hours. The weight was obtained daily before breakfast. Diuretics and other treatment deemed necessary were allowed during this period, but digitalis in any form was withheld. If it was suspected that digitalis had been given at any time during the two weeks before admission, the control period was prolonged for two to three weeks after the last dose to provide for elimination of the drug. In several instances the control period had to be terminated early where indications for the prompt administration of digitalis arose, such as a continued rise in heart rate and increase in signs of heart failure.

After stabilization of the patient's clinical status, the dose of digitoxin which had been decided upon was given. The need for additional doses during the first twenty-four hours was ascertained by observation of the patient several times daily. In order to calculate the pulse deficits, apical and radial pulse rates were recorded every two hours except at night during the first day of digitalization, and every four hours thereafter. An electrocardiogram was taken before digitalization, repeated several hours after the initial dose, again the following day, and thereafter as indicated. The patients were kept at bed rest throughout the period of digitalization and the period of ascertaining the maintenance requirements. Signs of digitalis intoxication were watched for.

OBSERVATIONS

Twelve patients (Table I) exhibiting auricular fibrillation who were given digitoxin are briefly presented to illustrate the effects obtained with certain amounts of the drug. In Cases 1, 3, and 4, digitoxin, 1.2 mg., was given in a single intravenous dose, with supplementary amounts to complete digitalization. In Cases 5, 6, 7, and 8, 1.2 mg. was given in a single oral dose and added amounts given to complete digitalization. In Cases 9, 10, 11, and 12, digitoxin, 1.8 mg., was given in one oral dose, with supplementary doses when digitalization had not been completed by this amount. Case 13 illustrates a patient who received 0.6 mg. intravenously, followed by 0.4 mg. by mouth, several hours later. A total of 2.8 mg. was ultimately required to digitalize this patient.

CASE 1 (394086) (Fig. 1, Table I).—A 45-year-old white woman, known to have had rheumatic heart disease since the age of 23, experienced palpitation, tachycardia, and a dull, aching sensation in the precordium ten days before admission to the hospital. Her weight was 59 kilograms. There was no dyspnea or cyanosis. A few fine râles were heard at both lung bases. The heart was enlarged to the left. There were typical signs of mitral stenosis and insufficiency. There was no edema or ascites. Auricular fibrillation with a ventricular rate of 125 per minute was present.

The patient was kept at rest in bed on a regular ward diet and fluids allowed as desired. After a four-day control period, when the heart rate was 120 per minute, digitoxin, 1.2 mg., was given in a single intravenous dose (Fig. 1). Twenty-four hours afterward the heart rate was 74 per minute. There were no symptoms of intoxication.

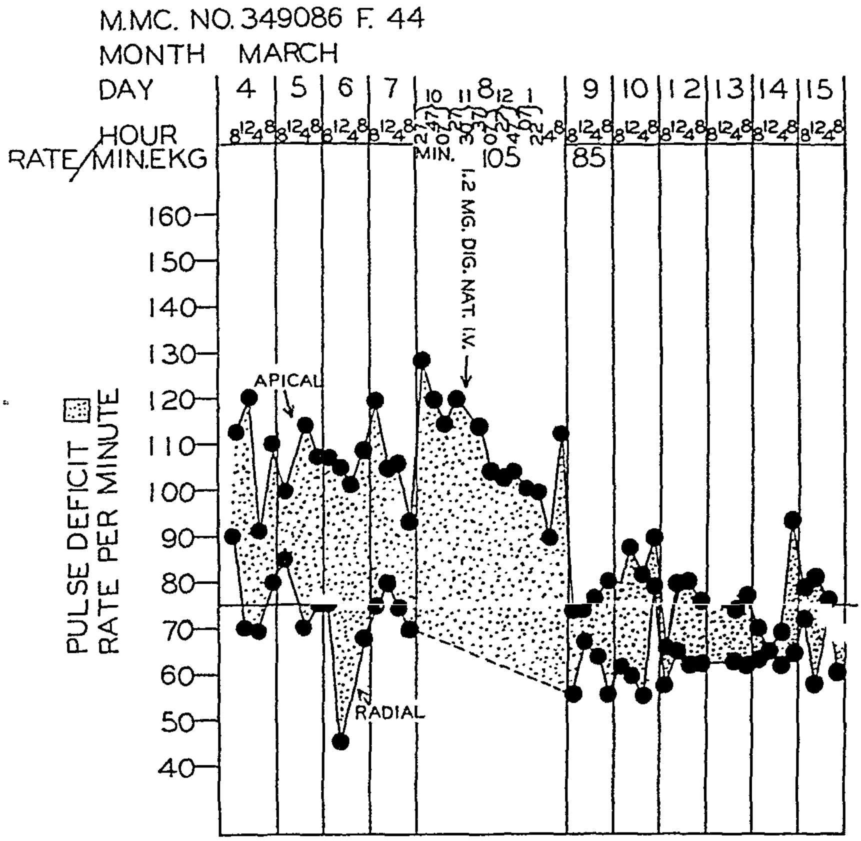


Fig. 1.—In this figure are shown data relating to Case 1, Patient M.Mc., to whom digitoxin, 1.2 mg., was given in one dose intravenously. In this chart, as well as in those which follow, the upper series of connected dots represent the apical heart rate and the lower series of dots, the radial rate, with stippled area indicating the pulse deficit. On the day digitalis was given, the minutes as well as the hours are recorded.

In this patient with a not too rapid ventricular rate, 1.2 mg. of digitoxin achieved adequate digitalization and slowed the heart rate to the sought-for level of 75 per minute. She was not given maintenance amounts of the drug, for we wished to follow the effect of this single dose.

Case 3 (28212) (Fig. 2, Table I).—A 35-year-old white housewife was admitted to hospital on Sept. 17, 1945, because of palpitation, dyspnea, and weakness of one month's duration. She had a history of rheumatic fever at 18 years of age and had been followed in the New York Hospital Cardiac Clinic since 1933. Physical examination revealed an enlarged heart with the characteristic murmurs of mitral insufficiency and stenosis. The rhythm was auricular fibrillation, the apical rate being 150 per minute, and the radial, 85 per minute. There was no edema. Her weight was 58.1 kilograms.

The patient was observed for six days while at bed rest. Fluids were limited to 1,500 cubic centimeters. During this time she lost 3.1 kilograms in weight and the cardiac rate was recorded between 110 and 150 per minute.

On the seventh hospital day, digitoxin 1.2 mg. was administered intravenously in one dose. This resulted in a fall in cardiac rate from 146 per minute to 90 per minute in two hours (Fig. 2). No symptoms of intoxication occurred. Twenty-four hours after the initial dose, the cardiac rate was 86 per minute with a pulse deficit of about 10 per minute. Forty-eight hours after the initial dose the heart rate had returned to 90 per minute and seventy-two hours after the initial

dose it was still at this figure. It was apparent that 1.2 mg. of the drug, although given intravenously in one dose, did not achieve satisfactory digitalization according to our standards. Digitalization was then completed by supplementary small oral doses of 0.2 to 0.4 mg. daily. A total of 2.2 mg. was given over five days to reduce the cardiac rate to 75 per minute. Slight nausea but no other symptoms occurred after a total of 2.4 mg. had been given. The patient was subsequently given 0.2 mg. as the maintenance amount.

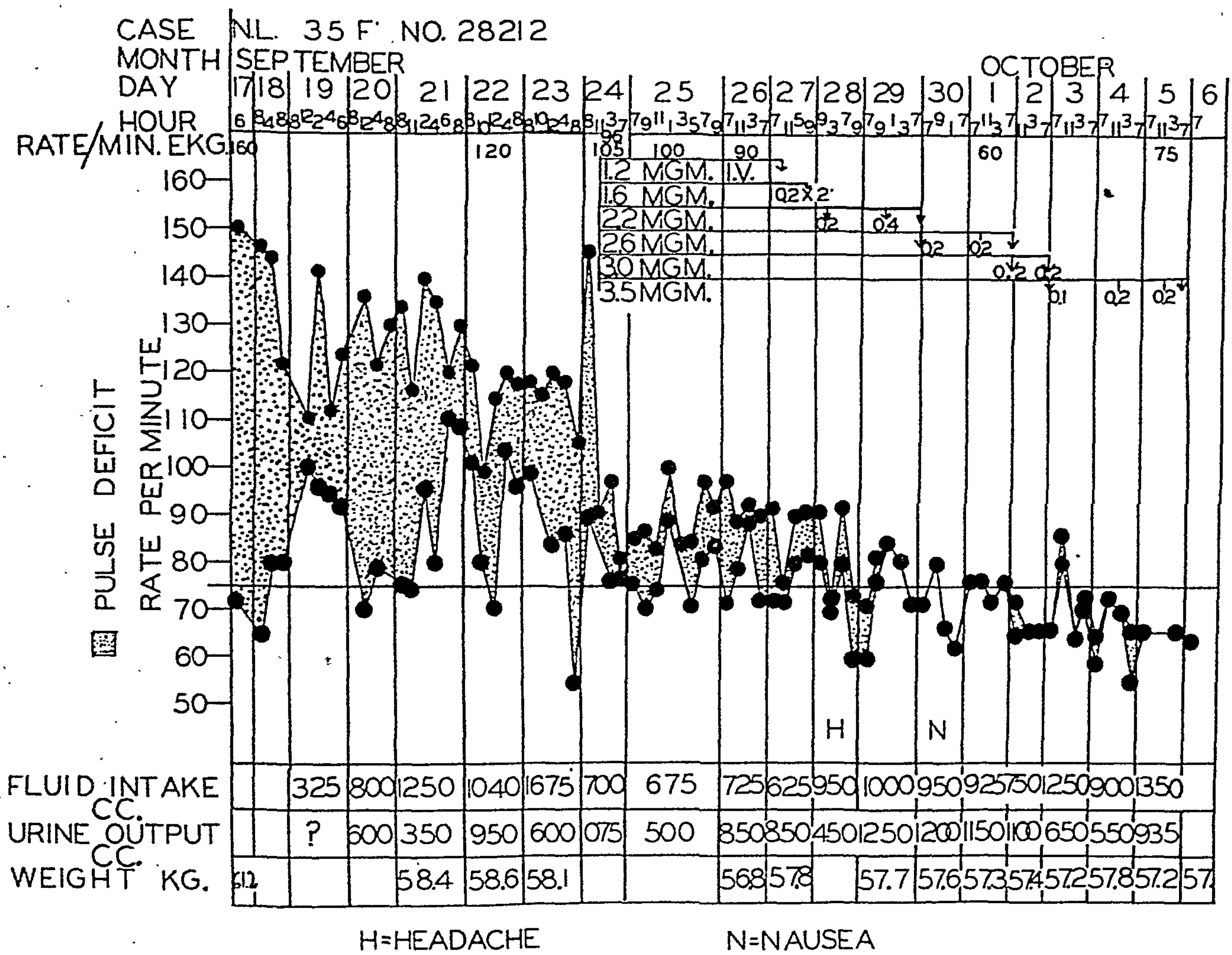


Fig. 2.—In this figure are shown data relating to Case 3, Patient N. L. Digitoxin, 1.2 mg., was given in an initial intravenous dose. Additional oral doses were given as indicated. In this chart and in those to follow, a vertical bar shows the time digitalis was first given. The amounts shown along this vertical line indicate the total amount of digitoxin which the patient received from the beginning to the end of the horizontal line with an arrow at the end. The time at which the additional amounts of drug were given is indicated by arrows from the horizontal line. In this manner of charting, the total amount of digitalis up to any one day and its distribution are readily apparent.

It is apparent that 0.2 mg. as a maintenance amount was too much since the heart rate continued to fall (Fig. 2). It is also apparent that 1.2 mg. given intravenously in one dose was insufficient to digitalize this patient, three days being allowed to observe its effects; that 1.6 mg. was inadequate; that 1.8 mg. was likewise insufficient; and that not until a total of 2.2 mg. had been given did the heart rate fall to a satisfactory level. It is estimated that 1.8 mg. would have been adequate if given in the first twenty-four hours (see p. 644), allowing the rest for maintenance over this period.

TABLE I. DATA RELATING TO THE AMOUNT OF DIGITALINE NATIVELLE RE

CASE	INITIALS	HISTORY NO.	ETIOL. DIAGNOSIS	ANAT. DIAGNOSIS	INITIAL DOSE (SINGLE) (MG.)	ROUTE DRUG GIVEN	DIVIDED DOSE SCHEME
1	M. McC.	349086	R.H.D.	M.S.M.I.E.H.	1.2	I.V.	
2	N. K.	381135	H.A.S.H.D.	(E.H.)	1.2	I.V.	
3	N. L.	28212	R.H.D.	M.S.M.I.E.H.	1.2	I.V.	
4	M. A.	84878	Hy.+R.H.D.	M.S.M.I.E.H.	1.2	I.V.	
5	W. L.	137050	A.S.H.D.	Myo.Fibr.	1.2	oral	
6	M. StL.	115465	H.A.S.H.D.	(E.H.)	1.2	oral	
7	K. C.	430023	Undeter.	? Cor.Pul.	1.2	cral	
8	M. H.	249105	A.S.H.D.	M.Scl. + calc. and E.H.	1.2	oral	
9	H. W.	433820	R.H.D.	M.S.E.H.	1.8	oral	
10	N. S.	229324	Hy.H.D.	(E.H.)	1.8	oral	
11	H. R.	443670	A.S.H.D.	(E.H.)	1.8	oral	
12	M. F.	365004	H.A.S.H.D.	(E.H.)	1.8	oral	
13	J. McC.	428209	A.S.H.D.	(E.H.) C.A.D. C.O.Myo.Fibr.		0.6 I.V. 0.4 oral	0.6 I.V. 0.4 oral
14	S. H.	332032	Hy.H.D.	(E.H.)		oral	0.4, 0.4, 0.2, 0.2
15	A. R.	254403	Hy.H.D.	C.A.D. (cor.scl.) (E.H.)		oral	0.4 × 3= 1.2
16	C. C.	219875	R.H.D.	M.S.M.I.A.S.A.I. E.H.		oral	0.2 × 7= 1.4
17	E. M.	388084	R.H.D.	?M.S.M.I.A.S.A.I. E.H.,B.B.B., C.A.D.		oral	0.2 × 6= 1.2
18	A. P.	298234	H.A.S.H.D.	(E.H.)		oral	0.2, 0.1
19	A. H.	339998	H.A.S.H.D.	(E.H.)		oral	0.2 × 10= 2.0
20	M. M.	19397	R.H.D.	(E.H.)M.S.M.I.A.I.		oral	
21	M. G.	376577	A.S.H.D.	(E.H.)		oral	0.5+0.3+0.2+0.2
22	L. S.	101768	R.H.D.	(?M.S.)M.I.E.H.		I.V.	0.4+0.8 I.V.
23	A. V.	423504	Hypth.A.S.H.D.	(E.H.)	1.2	oral	
24	G. O.	415472	Hypth.H.D.	(E.H.)	1.6	oral	
25	G. R.	426937	Hypth.H.D.		1.2	oral	
26	E. D.	441717	Hypth.A.S.H.D.	(E.H.)	1.2	oral	1.6 in 16 hrs.

R.H.D. = rheumatic heart disease; H.A.S.H.D. = Hypertensive arteriosclerotic heart disease; A.S. tension plus rheumatic heart disease; Hypth. = Hyperthyroid.

M.S. = mitral stenosis; M.I. = mitral insufficiency; A.S. = aortic stenosis; A.I. = aortic insuffi Cor.pul. = cor pumonale; C.O. = coronary occlusion.

I.V. = intravenously.

0 = none; + = yes; + to ++++ = degree.

CASE 4 (84878) (Fig. 3, Table I).—A 35-year-old white woman with known rheumatic heart disease who weighed 74.9 kilograms underwent bilateral lumbodorsal sympathectomy for essential hypertension on Dec. 5 and 17, 1945. The patient's course for the first forty-eight hours following the second operation was uneventful, but in the evening of the second postoperative day, the rhythm changed to auricular fibrillation with a ventricular rate of 130 per minute. There was no evidence of heart failure, and the patient was without symptoms.

It was decided to give 1.2 mg. of digitoxin intravenously in one dose at once (Fig. 3). Sixteen hours after this dose was given, the cardiac rate had only decreased to 94 per minute. There were no symptoms of intoxication. An additional oral dose of 0.4 mg. was given. This produced nausea and vomiting without affording full digitalization. An additional 0.2 mg. was given forty-eight hours after the initial dose, and the effect of a total 1.8 mg. was to slow the heart rate to

QUIRED TO DIGITALIZE TWENTY-SIX PATIENTS WITH AURICULAR FIBRILLATION

CASE	TOTAL DOSE TO DIGITALIZE IN TIME (COL. 11) (MG.)	INITIAL HEART RATE (MIN.)	FINAL HEART RATE (TIME OF TOTAL DOSE) (MIN.)	TIME REQUIRED TO SLOW RATE (HOURS)	ESTIMATED DIGITALIZING DOSE AFTER CORRECT. FOR AV. DAILY EXCRETION (MG.)	AV. DAILY MAINTENANCE DOSE (MG.)	DEGREE OF HEART FAILURE	WEIGHT (KG.)	TOXICITY FROM DIG.
1	1.2	128	76	24	1.2		0	59.0	
2	1.2	128	82	22			+	86.4	
3	2.2	146	72	120	1.8	0.1	0	58.1	+
4	1.8	130	74	72	1.7	0.1	0	73.9	+
5	2.2	145-120	74	60	2.0	0.1	0	50.4	+
6	3.3	150	76	168	2.4	0.1 - 0.2	++++	53.0	+
7	2.0	135	70	96	1.8	0.1 mg. q. 2 days	0	54.0	0
8	2.6	140	74	120	2.4	0.2	+++	40.0	+
9	1.8	140	70	12	1.8	0.1 - 0.2	0	58.4	?
10	5.0	136	75	15 days	2.9	0.1 - 0.2	++++	77.0	+
11	2.2	134	75	72	2.0	0.2	++	61.0	+
12	1.8	115	75	24	1.8	0.2	+++	38.2	0
13	2.8	128	74	156	2.1	0.1 - 0.2		?	0
14	3.6	136	76	176	2.2	0.1 - 0.2	++	75.0	
15	2.8	122	72	144	1.8	0.1 - 0.2	++	74.6	
16	1.8	126	76	84	1.6	>0.1	+	?	
17	2.3	143	76	144	1.7	0.1 - 0.2	0	59.5	
18	2.9	126	76	168	2.0	0.1 - 0.2	+++	52.0	
19	3.4	136	70	96	3.0	0.1	++	53.6	
20	2.3	210	72	39			+	74.0	
21	1.2	120	110	16			0	?	
22	1.2 (q.n.s.)	144	85-120	48		0.2	±	70.5	
23	3.4	142	75	96		0.1	0	45.3	
24	4.4	200	86	192		0.2	++++	58.0	
25	3.4	180	95	120			0	60.2	
26	1.6	120	82	24			0	38.6	

H.D. = Arteriosclerotic heart disease; HyH.D. = Hypertensive heart disease; Hy + R.H.D. = Hyper-

ciency; E.H. = enlarged heart; C.A.D. = coronary artery disease; Myo.Fibr. = myocardial fibrosis;

between 70 and 80 per minute. Maintenance doses averaging 0.1 mg. daily were continued. Headache, anorexia, and blurring of vision occurred on the seventh day of digitalis therapy, when the heart rate was 70 per minute. A total of 1.8 mg. given in forty-eight hours was necessary in this case to achieve full digitalization.

It is apparent (1) that 1.2 mg. given intravenously in one dose did not achieve adequate digitalization, (2) that a total of 1.6 mg. did not slow the heart rate sufficiently, but caused nausea and vomiting, and (3) that 1.8 mg. in forty-eight hours reduced the ventricular rate to around 75 per minute. The average maintenance amount was 0.1 mg.; if this is subtracted from 1.8 mg. as the maintenance amount in the second twenty-four hours of digitalization, it appears that

around 1.7 mg. would have been adequate to slow the rate if given in twenty-four hours.

Case 5 (137050) (Fig. 4, Table I).—An 86-year-old white man was admitted to hospital on Oct. 1, 1945, because of severe chest pain the night before admission. The patient had been followed in the New York Hospital Cardiac Clinic since 1933. The diagnosis was arteriosclerotic heart disease with an enlarged heart, pulmonary fibrosis, and emphysema.

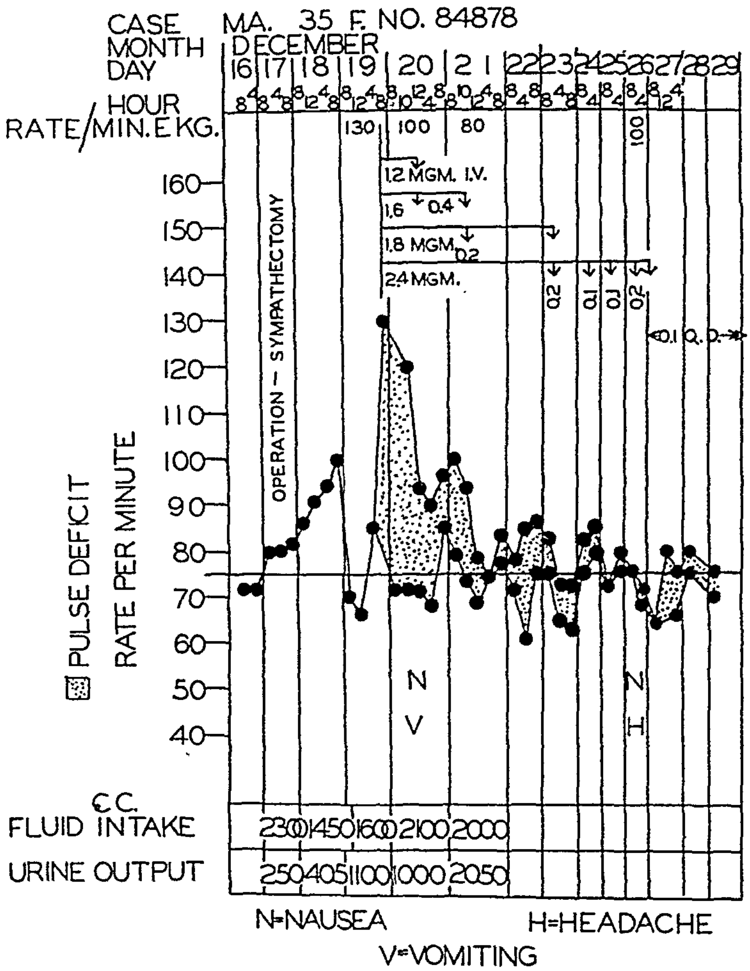


Fig. 3.—In this figure are shown data relating to Case 4, Patient M. A. Digitoxin, 1.2 mg., was given in an initial intravenous dose. Subsequent oral doses are shown.

There was no evidence of heart failure on admission. The blood pressure was 126/74. The lungs were clear. The heart was enlarged; auricular fibrillation with an apical rate of 140 per minute and a radial rate of 124 per minute were present. There was no edema. The patient weighed 50.4 kilograms.

The patient was observed for three days on a general diet and a limited fluid program without loss of weight. The apical heart rate fluctuated between 100 and 140 per minute with a pulse deficit ranging from 0 to 42 per minute. On the fourth hospital day, digitoxin 1.2 mg. was given in one oral dose (Fig. 4). This resulted in a fall in the cardiac rate from between 120 and 145 to 94 per minute in twelve hours and to 90 per minute in thirty-six hours. No symptoms of intoxication occurred. On the sixth hospital day, two days later, a total of 1.0 mg. of the drug was given in divided doses by mouth in an effort to complete digitalization. This induced nausea

The heart rate fell to 70 per minute. A total of 2.2 mg. of digitoxin in sixty hours was necessary for satisfactory digitalization. The patient was then given 0.1 mg. daily as the maintenance amount.

In this patient, 1.2 mg. by mouth in one dose in a man weighing only 50.4 kilograms was inadequate to achieve digitalization. The effect of this amount was observed during the following day. On the third day 1.0 mg. additional was given in divided doses and reduced the rate satisfactorily, making a total of 2.2 milligrams. This induced nausea. Since the average maintenance amount in this patient was 0.1 mg. daily, and 2.2 mg. was given over three days, if 0.1 × 2.0 is subtracted for the maintenance amount for the last two of these days, we arrive at 2.0 mg. as the digitalizing amount.

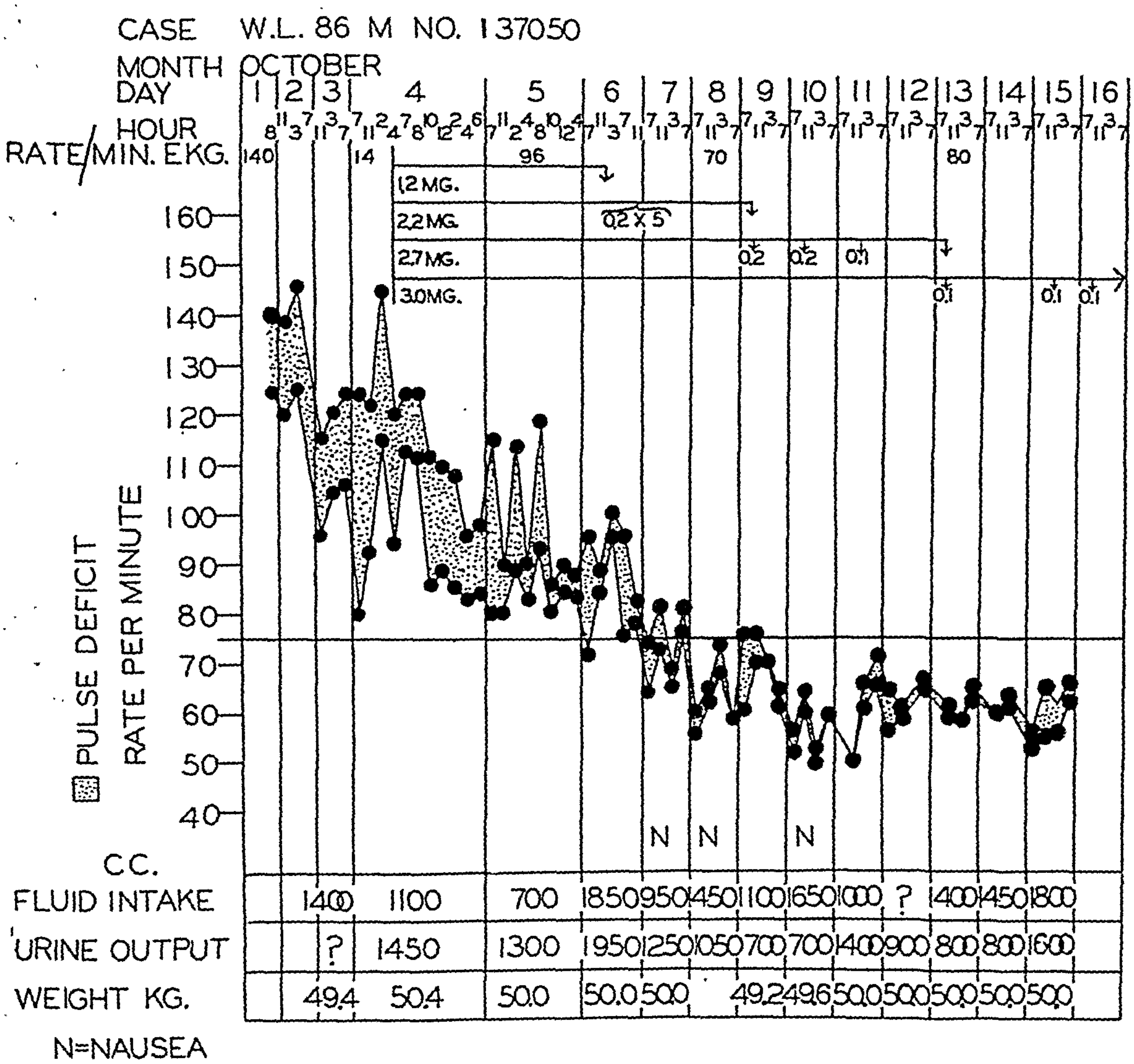


Fig. 4.—In this figure are shown data relating to Case 5, Patient W. L. Digitoxin, 1.2 mg., was given as an initial oral dose. Subsequent oral doses are shown.

Case 6 (115465) (Fig. 5, Table I).—A 76-year-old white woman was admitted to the hospital for the first time because of dyspnea, orthopnea, and swelling of the ankles. This was the first episode of cardiac decompensation. There was no previous history of rheumatic fever or hypertension. She weighed 53.0 kilograms. The neck veins were distended; she was moderately dyspneic and orthopneic. Moist râles were heard at both lung bases. The heart was enlarged to

the left. Auricular fibrillation was present with the ventricular rate of 150 per minute and radial rate of 126 per minute. The blood pressure was 190/120. The liver was enlarged and there was peripheral edema. The patient remained at bed rest for three days on a 3.0 Gm. salt diet and limited fluids. During this period the cardiac rate ranged between 114 and 150 per minute. The diagnosis was hypertensive and arteriosclerotic heart disease.

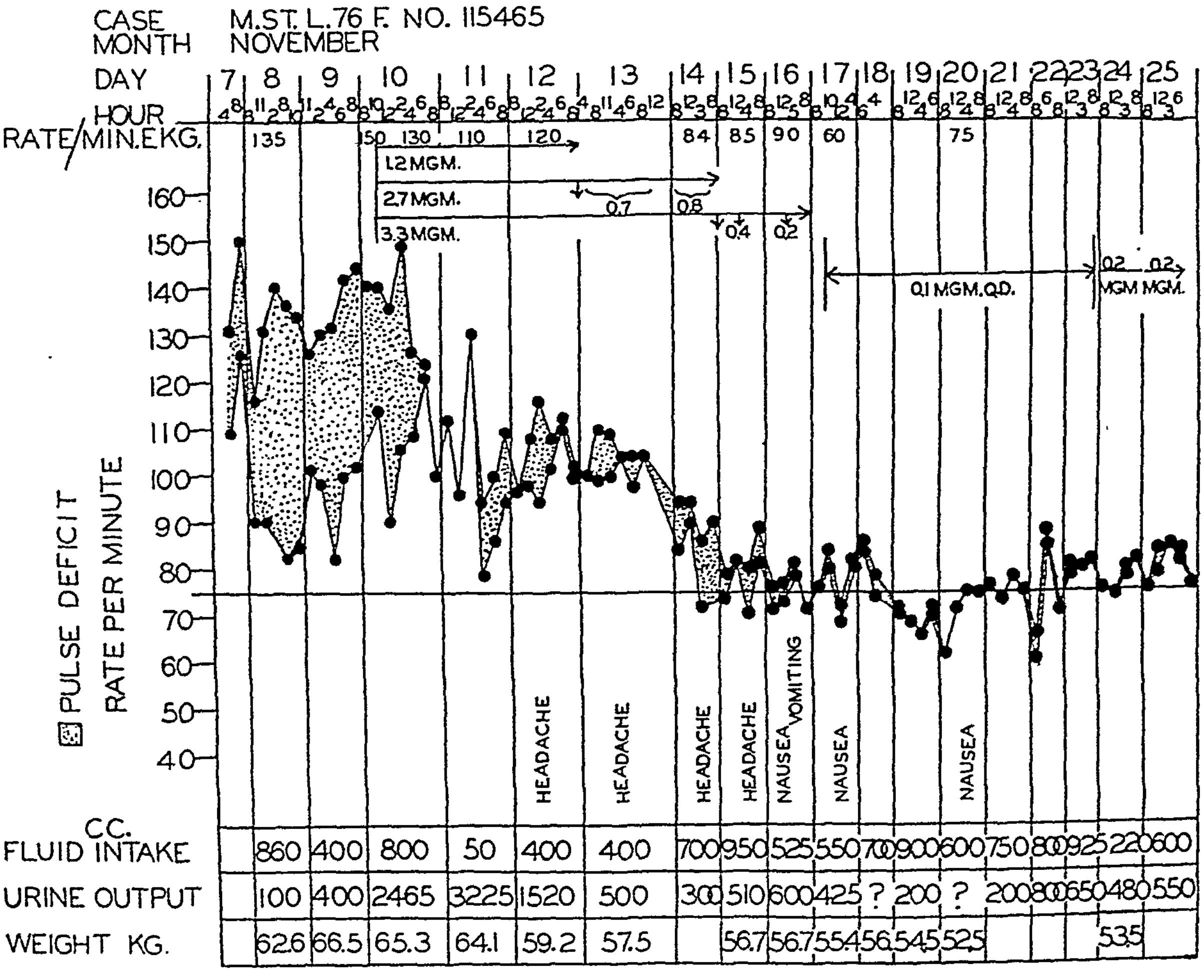


Fig. 5.—In this figure are shown data relating to Case 6, Patient M. St.L. Digitoxin, 1.2 mg., was given as an initial oral dose. Subsequent oral doses are shown.

On the fourth hospital day, digitoxin 1.2 mg., was given orally in one dose (Fig. 5). Twelve hours afterward the cardiac rate had fallen from 150 to 98 per minute. There were no symptoms of intoxication. Digitalis was not given for the next two days. During this time a weight loss of 4.9 kilograms occurred; slight edema remained and râles were still heard in the lungs. On the second day after the initial dose of digitoxin the patient complained of a slight headache, but the heart rate was 110 per minute. On the next day 0.7 mg. was given and 0.8 mg. on the following day, a total of 2.7 milligrams. Headache persisted, but no further symptoms of intoxication occurred. The heart rate fell to 90 per minute. In the following two days 0.6 mg. of digitoxin was given. A total of 3.3 mg. given in six days reduced the heart rate to 75 per minute. This produced nausea and vomiting. The patient was maintained for the next seven days on 0.1 mg. daily and was discharged on 0.2 mg. daily.

In this patient, weighing only 53.0 kilograms, 1.2 mg. in one dose by mouth was inadequate to achieve digitalization. The effect of this was observed for the two following days; the addition of 0.7 mg. and then 0.8 mg. on the fourth and fifth days, respectively, making a total of 2.7 mg., was not sufficient; not until 0.4 mg. and 0.2 mg. were given on the next two days, respectively, making a total of 3.3 mg. in seven days, was the rate reduced adequately. The maintenance amount in this patient was between 0.1 and 0.2 milligram. If the amount for six days' maintenance, 0.9 mg. (0.15 × 6), is subtracted from the total amount, we arrive at 2.4 mg. as the digitalizing amount for this patient if it had been given in twenty-four hours.

CASE 7 (430023) (Fig. 6, Table I).—A 55-year-old white housewife was admitted to hospital on Dec. 3, 1945, because of chills and fever, chest pain, and bloody sputum of one week's duration. This condition was associated with cough, dyspnea, and increasing orthopnea. Examination revealed an acutely ill woman who was dyspneic, orthopneic, and cyanotic. Her weight was 54.0 kilograms. Flatness, tubular breathing, and fine râles were present at the right lung base. The heart was enlarged. There was no edema. Auricular fibrillation with a ventricular rate of 130 per minute was present. An x-ray film of the chest exhibited dense annular shadows in the left

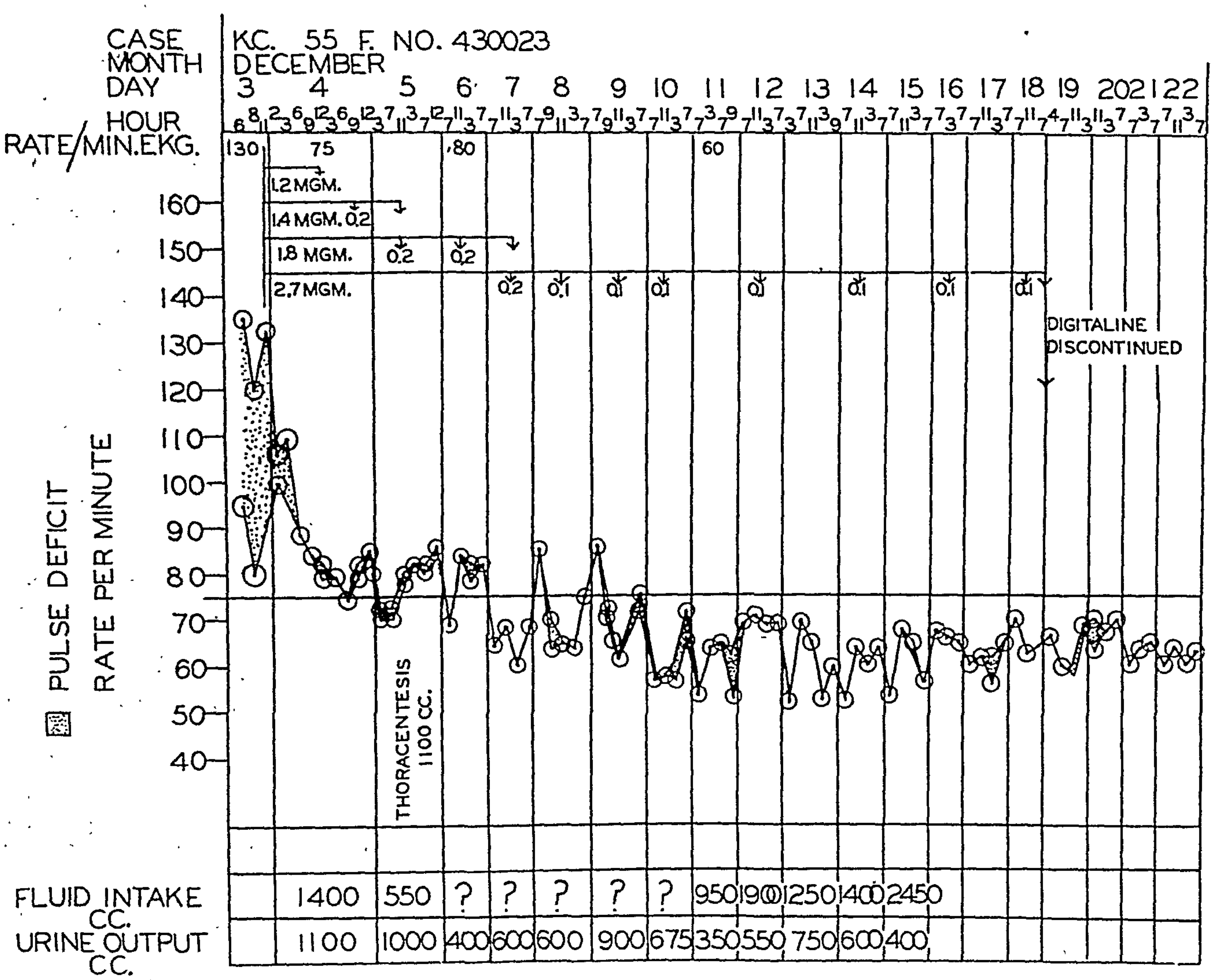


Fig. 6.—In this figure are shown data relating to Case 7, Patient K. C. Digitoxin, 1.2 mg., was given in an initial oral dose. Subsequent oral doses are shown.

paramediastinal area and right hilum with pleural effusion at the right base. The diagnosis was rheumatic heart disease with mitral stenosis and insufficiency, multiple pulmonary infarcts, and possibly pneumonia.

The patient was put at bed rest with fluids limited to 1,500 c.c. per day and given a 3.0 Gm. salt diet. The temperature was 102°F. on admission and ranged between 99.8 and 102° F. during the first week. Twenty thousand units of penicillin were given every three hours. One cubic centimeter of mercupurin was administered. The patient was put in an oxygen tent because of dyspnea. Digitoxin, 1.2 mg., was given in one oral dose without further delay (Fig. 6). The cardiac rate, which was 134 per minute, fell to 83 per minute twelve hours later. There were no symptoms of intoxication. Twelve hours after the initial dose 0.2 mg. were given, making a total of 1.4 mg., resulting in a fall in heart rate to 72 per minute. The rate rose again, however, and fluctuated between 72 and 86 per minute. No symptoms of overdosage occurred. A thoracentesis yielding 1,100 c.c. of serosanguinous fluid was performed to relieve the dyspnea. Digitoxin, 0.2 mg., was given daily for three days, but was reduced to 0.1 mg. because of a fall in heart rate below 70 per minute. During the last days of hospitalization, 0.1 mg. was given every other day and finally was discontinued, but auricular fibrillation persisted with a heart rate around 60.

One and two-tenths milligrams in one oral dose was not adequate to digitalize the patient, nor was 1.4 milligrams. After 0.2 mg. had been given daily for the next three days, making a total of 2.0 mg. in the four-day period, the ventricular rate remained at a satisfactory level. Since 0.1 mg. every second day was adequate maintenance in this patient, the maintenance amount over this four-day period was under 0.2 mg., making the digitalizing amount around 1.8 mg. if given in twenty-four hours (2.0 mg. less 0.2 mg.).

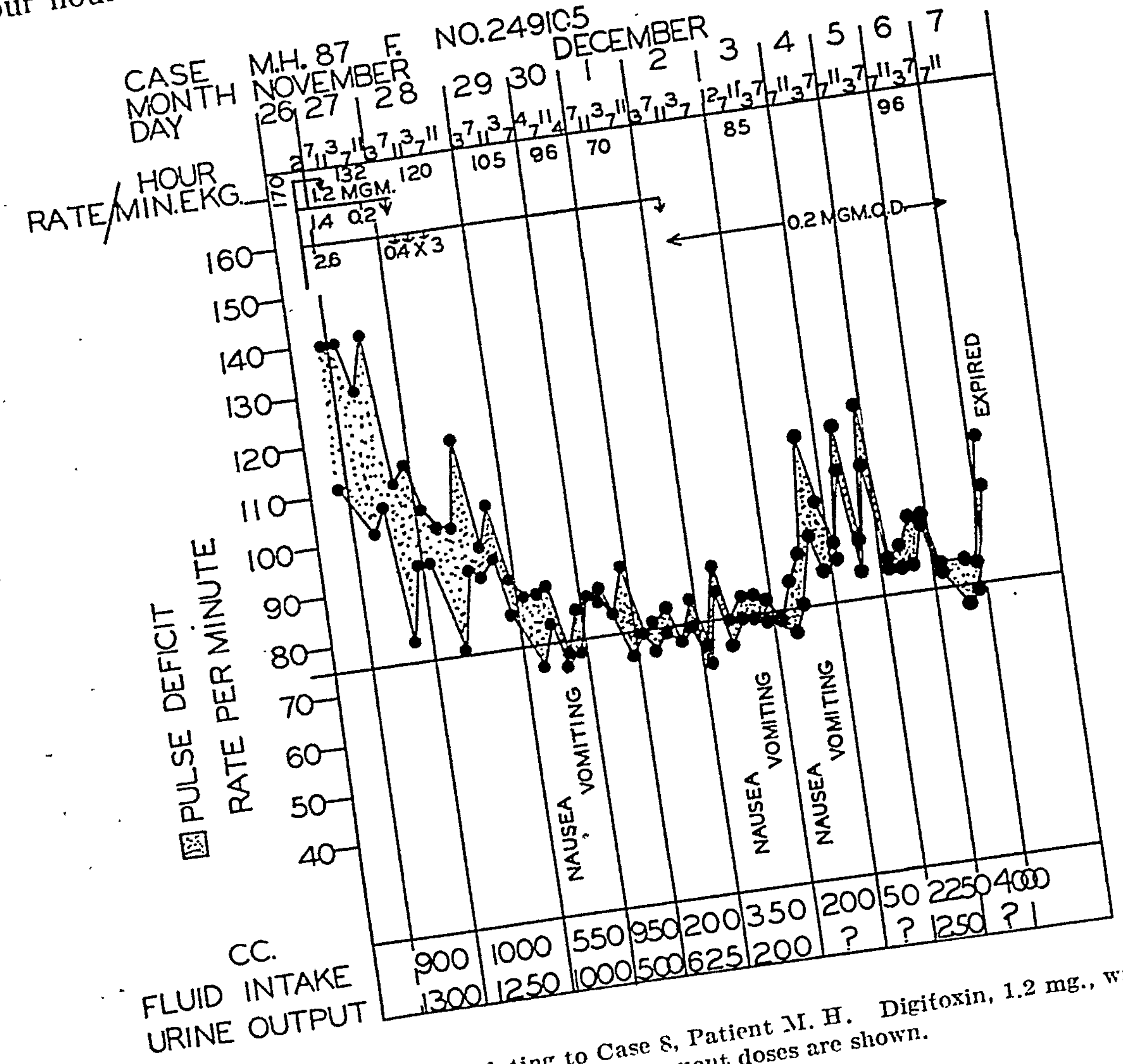
CASE 8 (249105) (Fig. 7, Table I).—An 85-year-old white housewife was admitted to the hospital because of dyspnea, weakness, fatigue, and swelling of the ankles of five or six days' duration.

The patient was very dyspneic and cyanotic; she appeared dehydrated. Her weight was 40.0 kilograms. Moist râles were heard at both lung bases, with pleural effusion at the right base. The heart was enlarged and auricular fibrillation with a ventricular rate of 140 per minute was present. The blood pressure was 190/100. There was moderate pitting edema of the ankles.

In view of her critical condition, the patient was digitalized immediately. Digitoxin, 1.2 mg., was given in one oral dose (Fig. 7). No further digitalis was given for the next nineteen hours, but during this time there was no appreciable fall in heart rate. Two-tenths milligram was then given by mouth. Twelve hours later the total effect of 1.4 mg. had reduced the cardiac rate to 100 per minute. No symptoms of overdosage had occurred. Three successive oral doses of 0.4 mg. of the drug were then given in an effort to bring the heart rate to 70 per minute. The following day, even though the heart rate had fallen only to 85 per minute, no digitalis was given because of nausea and vomiting. During the following three days no digitoxin was given, but the heart rate decreased to 75 per minute. A total of 2.6 mg. of digitoxin was required to reduce the heart rate to 74 per minute in 120 hours. The slow decline in the ventricular rate after the last of these doses was given indicates the continued induction of the effects of the drug after it was stopped. After four days without the drug, maintenance doses of 0.2 mg. daily were instituted, but nausea and vomiting occurred and dehydration developed. Parenteral fluids and other measures were without benefit; the heart rate increased in spite of maintenance amounts, and the patient expired on the eleventh hospital day.

It is apparent that 1.2 mg. given in one dose was inadequate, even though the patient weighed only 40.0 kilograms; that 1.4 mg. in the first twenty-four hours was insufficient, and that the addition of 1.2 mg. more, making 2.6 mg. given in two days, was the adequate amount. Nausea and vomiting occurred on the third day, indicating the slow absorption. The range between the amount

required to produce adequate slowing and that required to induce nausea and vomiting in this patient was narrow. Since a total of 2.6 mg. given in two days was adequate to slow the ventricular rate and 0.2 mg. may be taken as the maintenance amount on this second day, the digitalizing amount if given in twenty-four hours would have been around 2.4 milligrams.



g. 7.—In this figure are shown data relating to Case 8, Patient M. H. Digitoxin, 1.2 mg., was given in an initial oral dose. Subsequent doses are shown.

CASE 9 (433820) (Fig. 8, Table I).—A 31-year-old white man was in good health until six weeks before admission when he suffered from sore throat with fever. He subsequently developed exertional dyspnea and noticed rapid beating of the heart. There was no previous history of rheumatic fever. Two weeks before admission he was given digitalis, but had stopped the drug several days before admission. Examination revealed a well-developed white man, weighing 58.4 kilograms, without dyspnea or cyanosis. The lungs were clear. The heart was slightly enlarged. The cardiac rhythm was auricular fibrillation; the ventricular rate was 150 per minute, and the radial, 85 per minute. There was no edema. A diagnosis of rheumatic heart disease with mitral stenosis and insufficiency was made.

The patient was kept at bed rest on a 3.0 Gm. salt diet and fluids limited to 1,500 c.c. for four days. The apical heart rate fluctuated between 100 and 140 per minute during this period. Because the ventricular rate had increased so much on the fifth hospital day, the patient was given digitoxin 1.8 mg. in one oral dose (Fig. 8). This amount induced a fall in heart rate from 140 to 70 per minute at the end of six hours. No symptoms of intoxication occurred. After twelve

hours the heart rate was still 70 per minute with a pulse deficit of 8 beats per minute. Because of beginning increase in heart rate twenty-four hours after the initial dose was given, 0.2 mg. was given. The patient was then maintained on 0.2 mg. and 0.1 mg. on alternate days, and although there were wide daily fluctuations in heart rate, the basal heart rate remained about 70 per minute.

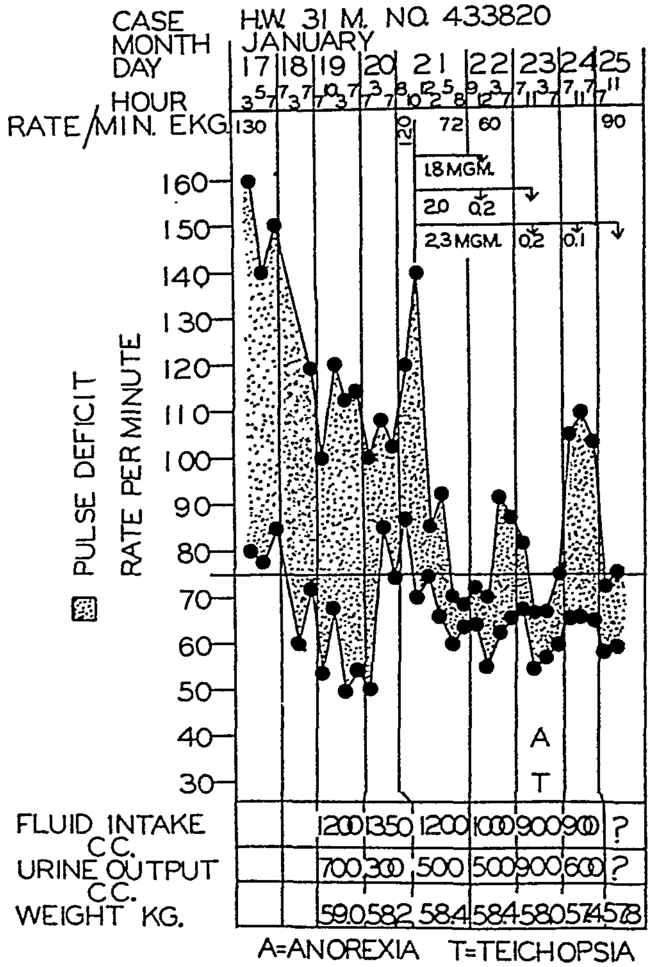


Fig. 8.—In this figure are shown data relating to Case 9, Patient H. W. Digitoxin, 1.8 mg., was given in an initial oral dose. Subsequent doses are shown.

One and eight-tenths milligrams of digitoxin in one dose by mouth produced full digitalization with only slight anorexia and yellow vision.

Case 10 (229324) (Fig. 9, Table I).—A 64-year-old white woman, with known hypertension for nineteen years, was admitted to hospital on Feb. 27, 1946, because of progressive dyspnea, orthopnea, and ankle edema of three weeks' duration following an upper respiratory infection. Three months before admission digitalis had been prescribed, but none had been taken for two months.

The patient weighed 77.0 kilograms and exhibited dyspnea and slight cyanosis. There was flatness at the right lung base, and moist râles were heard throughout both lung fields. The heart was enlarged to the left. The cardiac rhythm was auricular fibrillation; the apex rate was 130 per minute and the radial rate, 88 per minute. Ascites and moderate pitting ankle edema were present.

The patient was kept at bed rest on a 3.0 Gm. salt diet for two days. The heart rate fluctuated between 155 and 115 per minute. On the third day, digitoxin, 1.8 mg., was given in one oral

dose (Fig. 9). The heart rate fell from 136 to 120 per minute in twelve hours. In an effort to complete digitalization, 0.4 mg. was then given. The effect of a total of 2.2 mg. in twenty-four hours was to slow the cardiac rate to only 98 per minute. Moderate nausea developed at this time. A supplementary small dose of 0.2 mg. reduced the heart rate to only 95 per minute. Anorexia, without other symptoms of digitalis intoxication, persisted. A weight loss of 8.0 kilograms occurred, however, over the three-day period of digitalization, and edema nearly disappeared. The patient received 0.2 mg. daily thereafter (except on the ninth day after digitalization was started, when she received 0.4 mg.), but a cardiac rate of 80 per minute was not recorded until 3.8 mg. of digitoxin had been given over a nine-day period. On maintenance amounts of 0.2 mg. the rate continued to become slower and finally leveled around 75 per minute on the fifteenth day of therapy.

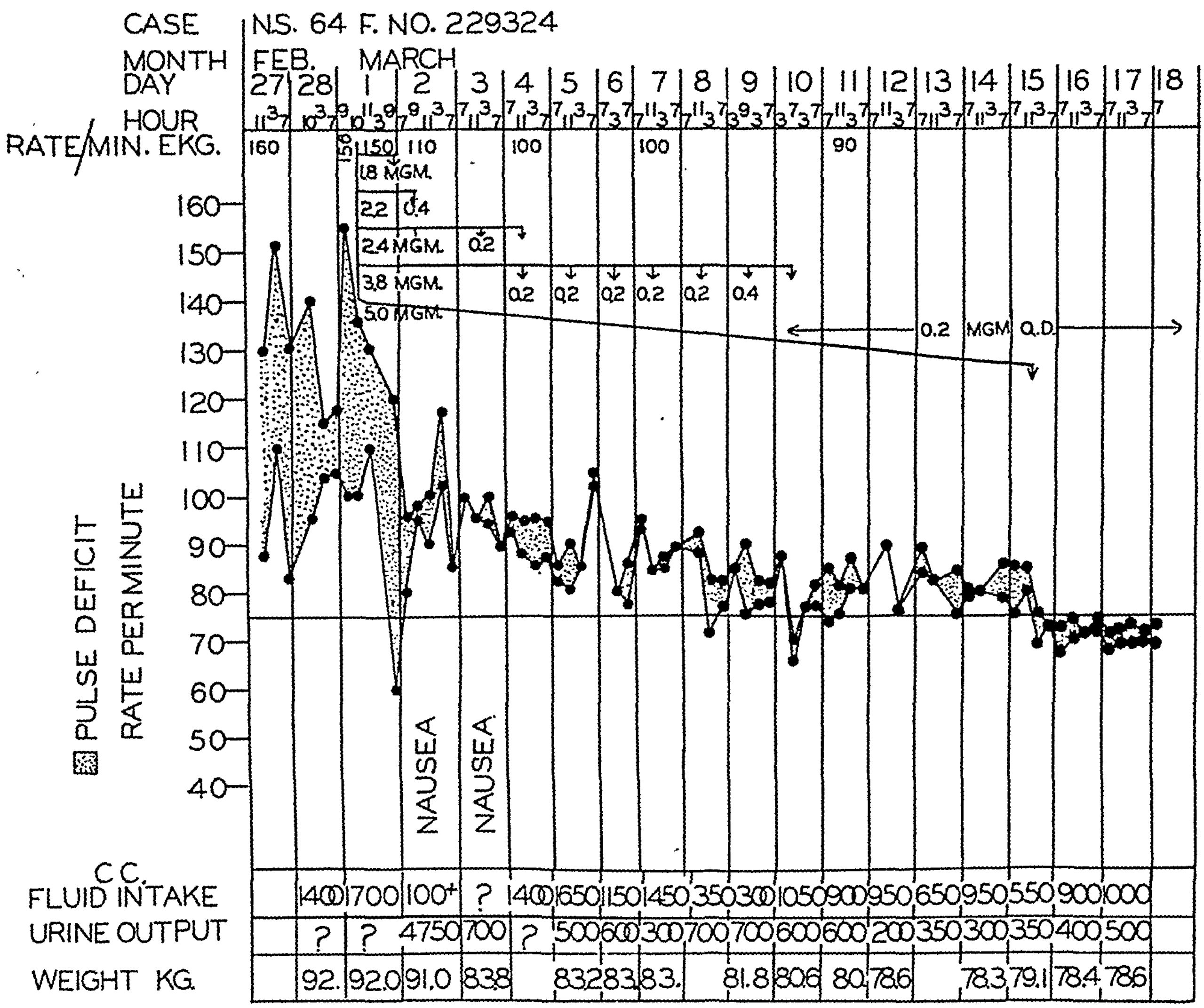


Fig. 9.—In this figure are shown data relating to Case 10, Patient N. S. Digitoxin, 1.8 mg. was given in an initial oral dose. Subsequent oral doses are shown.

It is apparent that 0.2 mg. was too much for maintenance and that the patient during this time was not adequately digitalized and was using some of the maintenance amount for digitalization. If 0.1 mg. alternating with 0.2 mg. was enough for maintenance (0.2 mg. being too much) and over the period of fifteen days the patient was given a total of 5.0 mg., 2.1 mg. of this (0.15 mg. × 14 days) was used for maintenance, leaving 2.9 mg. for digitalization if it had

been given in twenty-four hours. It is apparent from the chart that 1.8 mg., 2.2 mg., and 2.4 mg. were all inadequate, in agreement with the calculation that around 2.9 mg. was the digitalizing amount.

CASE 11 (443670) (Fig. 10, Table I).—A 70-year-old white woman was admitted to the hospital on May 3, 1946, with a history of increasing dyspnea and fatigue. During the week before admission there were several attacks of nocturnal dyspnea. The patient had been taking a liquid preparation of digitalis at times, but had received none during the two weeks before admission.

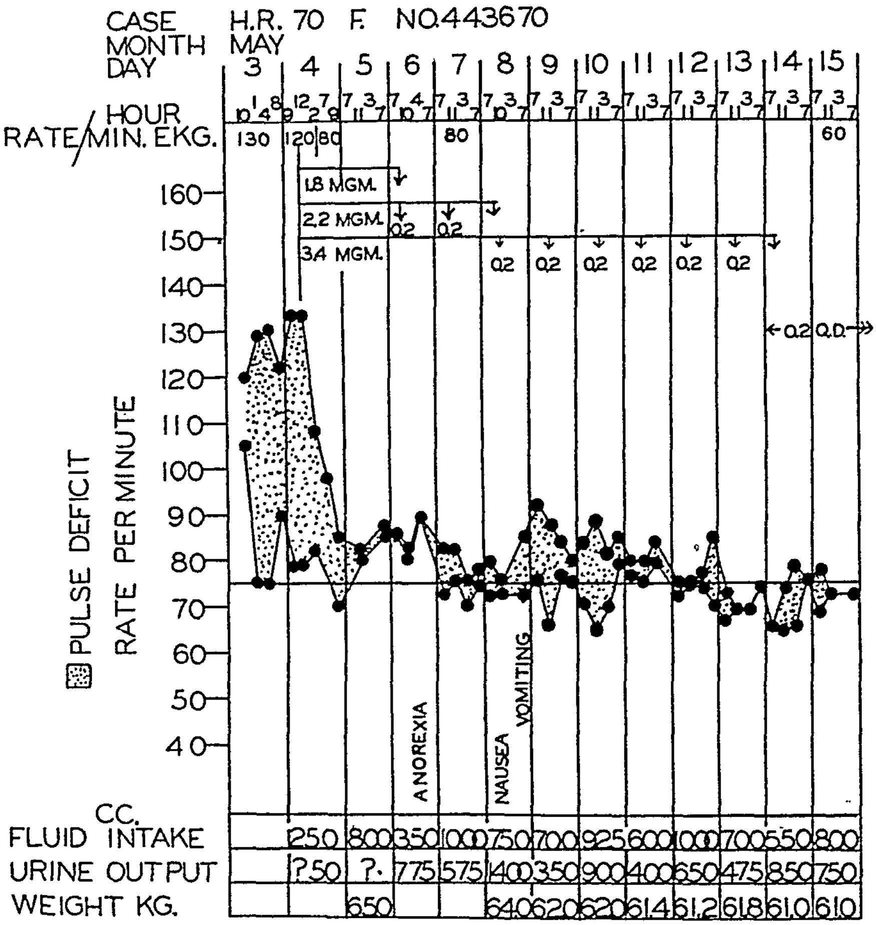


Fig. 10.—In this figure are shown data relating to Case 11, Patient H. R. Digitoxin, 1.8 mg., was given in an initial oral dose. Subsequent oral doses are shown.

The patient weighed 61.0 kilograms. Many moist râles were audible in the lower one-half of both lung fields. The cardiac rhythm was auricular fibrillation, with an apical rate of 135 per minute and a radial rate of 75 per minute. No murmurs were heard. There was no edema.

The patient was observed at bed rest with a 3.0 Gm. salt diet and fluids limited to 1,400 c.c. in twenty-four hours. She received 0.5 Gm. aminophylline to relieve the dyspnea. On the following day when the cardiac rate was 134 per minute, digitoxin, 1.8 mg., was given orally in one dose (Fig. 10). After twenty-four hours the heart rate had fallen to 82 per minute. No digitalis was given for the next twenty-four hours, and forty-eight hours after the initial dose of 1.8 mg. the heart rate was 86 per minute. Two-tenths milligram was then given on two successive days, which reduced the heart rate to 76 per minute. Anorexia was observed after 1.8 mg. and nausea and vomiting occurred after 2.2 milligrams. The patient was maintained on 0.2 mg. and râles

in the chest slowly disappeared. A total of 2.2 mg. of digitoxin was required in this case to produce full digitalization.

In this patient, 1.8 mg. in one oral dose was not sufficient to slow the ventricular rate. The effect was observed for two days before additional amounts were given. The use of 0.2 mg. daily finally reduced the rate to around 75 per minute. It is likely that 0.2 mg. was slightly too much as the maintenance amount since further slowing took place with its use. It was calculated that around 2.0 mg. would have been adequate if given in twenty-four hours.

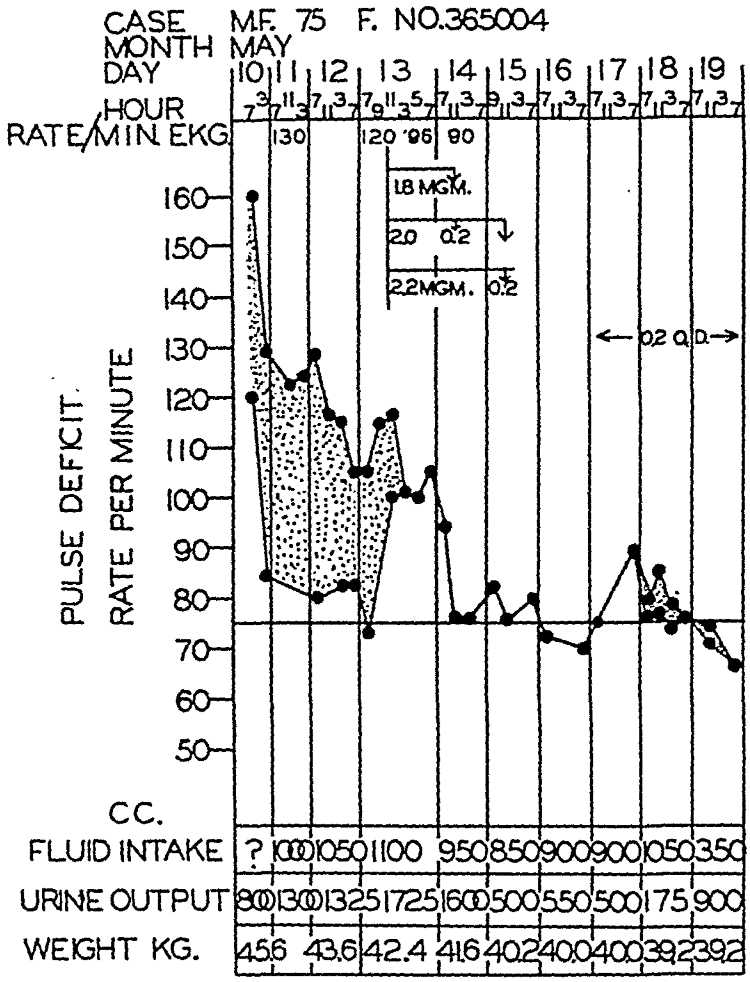


Fig. 11.—In this figure are shown data relating to Case 12, Patient M. F. Digitoxin, 1.8 mg., was given in an initial oral dose. Subsequent oral doses are shown.

CASE 12 (365004) (Fig. 11, Table I).—A 70-year-old white woman was admitted to the hospital on May 10, 1946, because of progressive dyspnea, orthopnea, and edema of the ankles of ten days' duration. The patient was known to have had hypertension for many years, but had remained free of symptoms until the present illness. The patient was dyspneic and orthopneic on admission, and the neck vessels appeared distended. She weighed 38.2 kilograms. A few moist râles were heard throughout both lungs. The cardiac rhythm was auricular fibrillation with an apical rate of 160 per minute. The heart was enlarged to the left. The liver was palpable three fingerbreadths below the costal margin. There was marked pitting edema of the ankles.

The patient was kept at bed rest and given a diet containing 3.0 Gm. of salt. The fluids were limited to 1,500 cubic centimeters. The control period was of three days' duration. During this

time she lost 3.2 kilograms in weight, the dyspnea decreased, and the heart rate fell from the admission rate of 160 per minute to range between 115 and 130 per minute, with a wide pulse deficit. On the fourth hospital day she received digitoxin, 1.8 mg., in one oral dose (Fig. 11). A fall in heart rate from 115 to 76 per minute in twenty-four hours occurred. There were no symptoms of intoxication. The dyspnea and edema disappeared without the use of other diuretics. She was given maintenance amounts of 0.2 mg. daily.

Full digitalization without symptoms of overdosage was obtained in this patient with one oral dose of 1.8 mg. of digitoxin. It is to be recalled that this patient weighed only 38.2 kilograms.

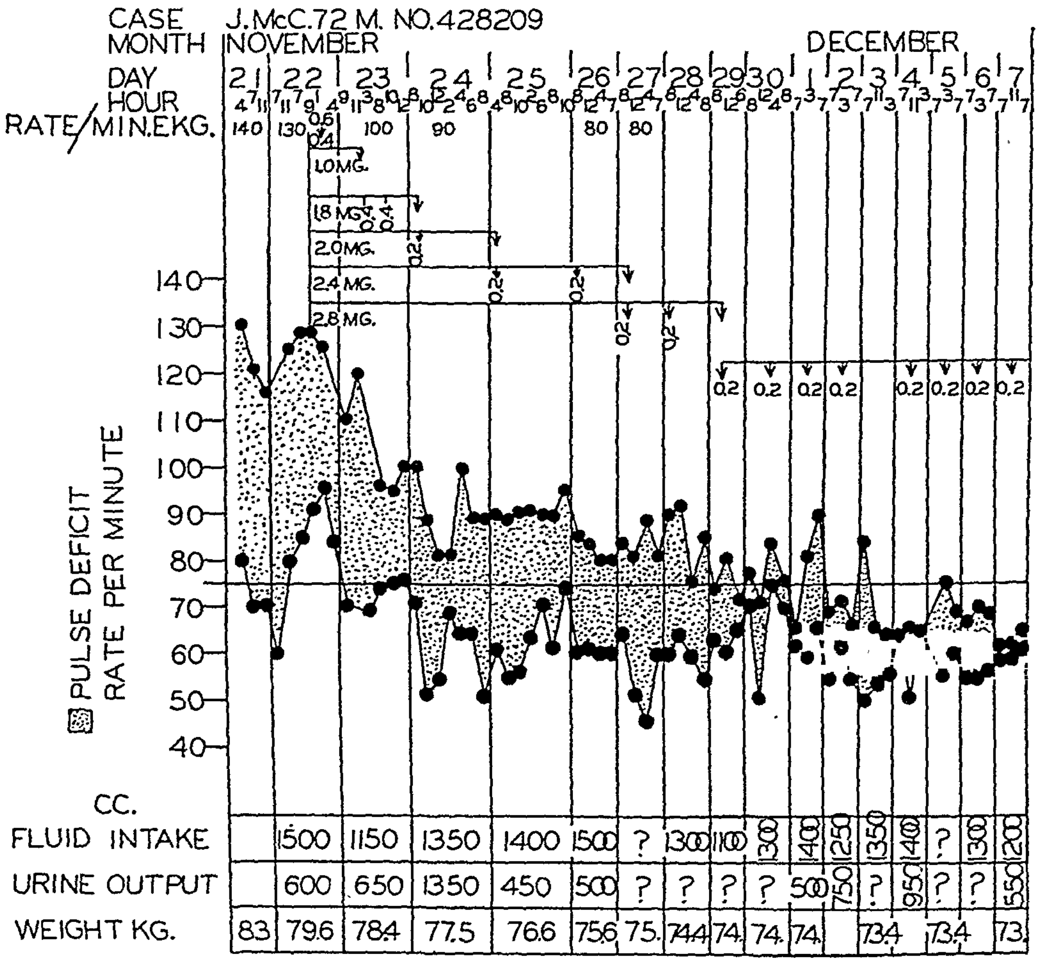


Fig. 12.—In this figure are shown data relating to Case 13, Patient J. McC. Divided doses of digitoxin were given as indicated and subsequent oral doses were given as recorded in the chart.

Case 13 (428209) (Fig. 12, Table I).—A 72-year-old white janitor was admitted to the hospital on Nov. 21, 1945, with a history of rapid heart beat, progressive dyspnea, and orthopnea of five months' duration. The patient experienced frequent attacks of precordial pain relieved by alcohol or rest. He was dyspneic, orthopneic, and cyanotic. The blood pressure was 100/70. Moist râles were heard at the bases of both lungs. The cardiac rhythm was auricular fibrillation, with an apical rate of 130 per minute and a radial rate of 70 per minute. The liver was palpable three fingerbreadths below the costal margin. There was a moderate degree of ankle edema. The diagnosis was arteriosclerotic heart disease with enlarged heart, coronary artery disease, and possible recent myocardial infarction.

The patient was given 0.5 Gm. of aminophylline and oxygen by mask to relieve the dyspnea. A 3.0 Gm. salt diet and restriction of fluids to 1,500 c.c. daily were ordered. It was planned to obtain several days of bed rest alone on this regimen to stabilize the heart rate, but because of a sudden severe attack of pulmonary edema thirty hours after admission, digitoxin 0.6 mg. was given intravenously, followed in three hours by an oral dose of 0.4 mg. (Fig. 12). After twelve hours the cardiac rate had fallen only to 120 per minute. During the second day of digitalization, 0.8 mg. additional was given, making a total of 1.8 milligrams. The following day 0.2 mg. additional was given. A total of 2.0 mg. of the drug had reduced the heart rate to only 90 per minute, but had not induced symptoms of overdosage. Subsequent small oral doses were given totaling 2.8 mg. over a six and one-half day period (Fig. 11), which represented the amount required to reduce the heart rate to 75 per minute to complete digitalization and afford maintenance. The patient was maintained on 0.2 mg. daily, except on the eleventh day after digitalization when the drug was omitted.

It is apparent that a total of 1.0 mg. orally and intravenously was insufficient to slow the rate, that the total of 1.8 mg. on the second day was inadequate, as was the total of 2.0 mg. on the third day, and so on. The rate had slowed to 75 per minute on the sixth day after a total of 2.8 milligrams. That slowing continued to occur on 0.2 mg. every day indicated that some was being used for increasing digitalization and some for maintenance, 0.2 mg. being too much for maintenance. If 0.15 mg. daily is allotted to maintenance for the five days of the six that the total of 2.8 mg. was given, we arrive at 2.1 mg. which, if given in twenty-four hours, would have digitalized this patient. That this was near the amount is indicated by the amounts which were inadequate.

Comment.—A review of the records of twenty-two hospital patients who had auricular fibrillation for which they received digitoxin disclosed that 1.2 mg. of the drug given within a twenty-four hour period generally failed to reduce the heart rate to between 70 and 75 per minute. In this analysis, the records of patients suffering from hyperthyroidism were excluded. Fourteen patients received digitoxin, 1.2 mg. (Cases 1, 2, 3, 4, 5, 6, 7, 8, 14, 15, 17, 20, 21, and 22); nine patients received the drug by mouth (Cases 5, 6, 7, 8, 14, 15, 17, 20, and 21); and five, intravenously (Cases 1, 2, 3, 4, and 22, Table I). In none of the patients who took this amount by mouth was the heart rate reduced to between 70 and 75 per minute. In one patient only was 1.2 mg. intravenously adequate (Case 1). It was noted that, in general, patients whose initial heart rates tended to be low required less digitoxin to reduce the ventricular rate to about 70 per minute. Thirteen patients, therefore, of the fifteen receiving 1.2 mg. were not adequately digitalized by this amount (Cases 2, 3, 4, 5, 6, 7, 8, 14, 15, 17, 20, 21, and 22, Table I). There was no correlation between weight of the patients and the amount of drug required to reduce the heart rate; the heart rates of the patients who weighed less were not reduced further than were the rates of the heavier patients by a given dose of digitoxin (Table I).

Four patients with auricular fibrillation were given 1.2 mg. of digitoxin in a single oral dose (Cases 5, 6, 7, 8, Table I). In none of these patients was this dose adequate for full digitalization. Supplemental oral doses were required to complete digitalization in all four patients. No evidence of digitalis intoxication occurred with 1.2 mg. of the drug.

Four patients with auricular fibrillation were given digitoxin, 1.2 mg., in a single dose intravenously (Cases 1, 2, 3, and 4). In one of these the ventricular rate was reduced to 76 per minute (Case 1); in the other three the heart rate remained above 80 per minute. Adequate digitalization was, therefore, achieved in only one of the four patients. Symptoms of intoxication occurred only once when the drug was given in this manner (Case 4). It appears, therefore, that digitalization was not obtained with 1.2 mg. in a greater proportion of patients when the drug was administered by vein than when it was given orally. It is recognized, however, that the number of cases in which this comparison is made is small.

In six patients digitalization was begun by an initial dose of 1.2 mg. and completed by supplementary doses (Cases 3, 4, 5, 6, 7, and 8). In these patients 1.2 mg. of the drug proved inadequate to digitalize, and supplementary doses were given until the heart rate fell to approximately 70 per minute. It was found that amounts totaling between 1.8 and 5.0 mg. of the drug were required to achieve digitalization in these patients in from three to fifteen days.

Four patients with rapid auricular fibrillation were given digitoxin, 1.8 mg., in a single oral dose (Cases 9, 10, 11, and 12). In two patients this amount was adequate to reduce the heart rate to 75 per minute (Cases 9 and 12). In a third patient (Case 11) 2.2 mg. of the drug were required to bring the cardiac rate below 80 per minute, and in the fourth patient (Case 10), a total of 5.0 mg. given in fifteen days was needed to complete digitalization. Symptoms of intoxication that might be ascribed to overdosage occurred in three patients (Cases 9, 10, and 11).

Ten patients with rapid auricular fibrillation received digitoxin in divided doses (Cases 13, 14, 15, 16, 17, 18, 19, 20, 21, and 22, Table I). Within the first twenty-four hours 1.2 mg. of the drug were given in several doses, but full digitalization usually was not obtained in these patients until they had been receiving the drug for several days. Corrections for daily excretions of the drug based on daily maintenance requirements allow us to arrive at an estimation of the total amount of the drug needed for digitalization if it had been given in twenty-four hours. In none of the patients was 1.2 mg. found to be adequate to reduce the heart rate to about 75 per minute. In these patients, amounts totaling from 1.8 to 3.6 mg. were required for full digitalization. The average digitalizing dose for these patients was 2.1 milligrams. Case 13 (Fig. 12, Table I) is representative of this group.

In Table I are shown the amounts of digitoxin required to achieve full digitalization in Cases 1 to 19 inclusive (excluding Case 2) with auricular fibrillation. In a number of instances digitalization was achieved only after the drug had been given for several days. In calculation of the total dose of digitoxin required in these cases, corrections for daily excretion of the drug were made. Excretion was estimated by the average amount of the drug, over a period of time, which was needed for daily maintenance after digitalization had been completed. Daily maintenance doses ranged from less than 0.1 up to 0.2 mg. daily, averaging around 0.15 mg. daily for all of the cases. The frequency curve of the amount is shown in Fig. 13,*C*. The total doses for digitalization, corrected for daily drug

excretion, appear in the appropriate column of Table I. The average corrected total dose of digitoxin required for digitalization in ten patients (Cases 3 to 12, inclusive) given 1.2 mg. and 1.8 mg. in one dose, followed by sufficient drug to achieve digitalization, was 2.06 mg., the range being 1.7 to 2.9 milligrams. If the one patient (Case 1) in whom 1.2 mg. intravenously was adequate were included, the average would be 1.98 mg., in short, 2.0 milligrams. The average for seven patients (Cases 13 to 19, inclusive) in whom the drug was given in divided doses was 2.06 mg., the range being 1.6 to 3.0 milligrams. The average for the eighteen patients was 2.01 milligrams. The amount required to digitalize when a large amount was given first, or when given in smaller amounts, turned out

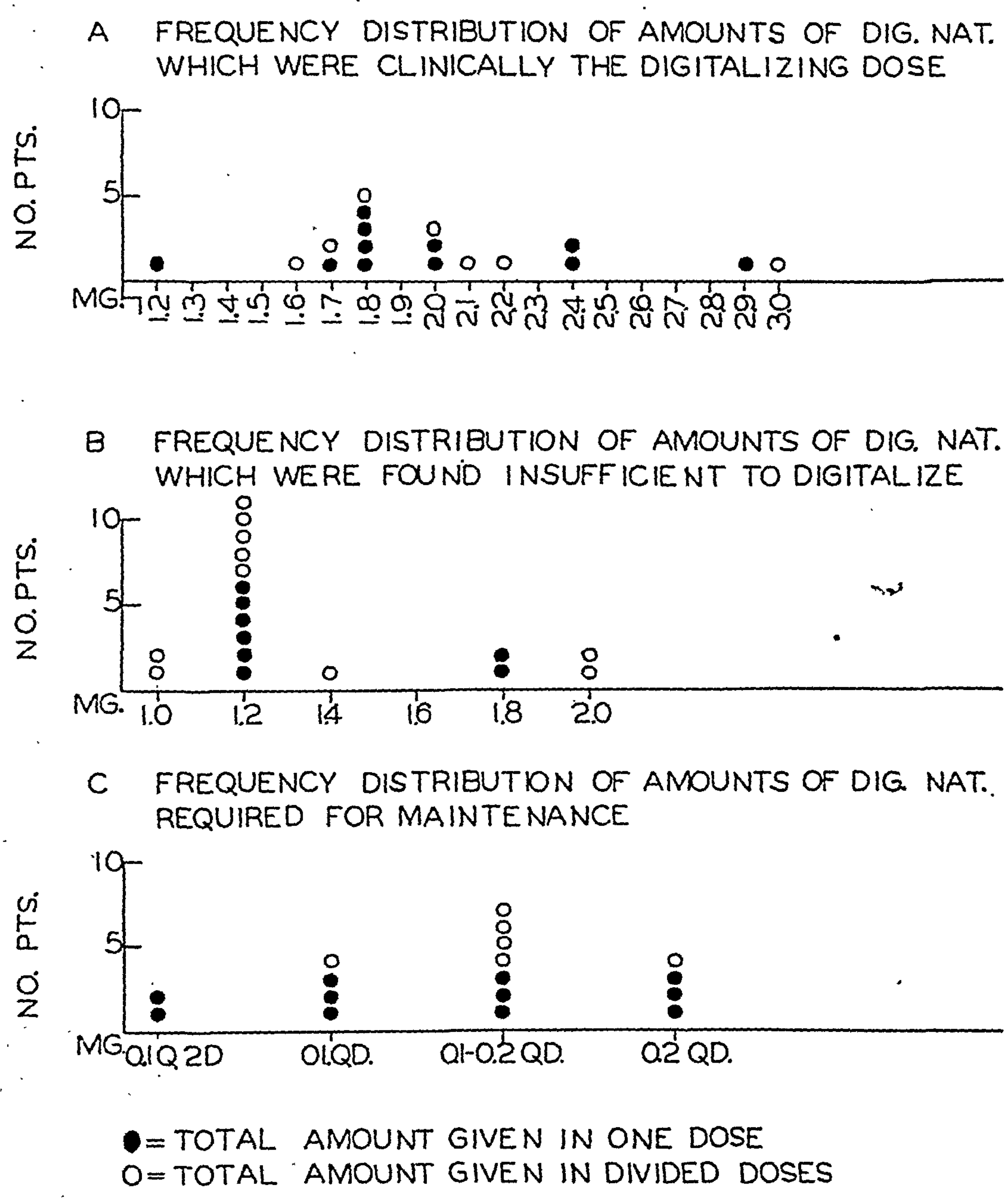


Fig. 13.—*A*, The frequency distribution of amounts of digitoxin which were clinically the digitalizing amount in eighteen patients. *B*, The frequency distribution of amounts of digitoxin which were found insufficient to digitalize eighteen patients. *C*, The frequency distribution of amounts of digitoxin which were required for maintenance in seventeen patients.

to be approximately the same, namely, 2.0 milligrams. There was no significant difference between the amount required when part was given intravenously. The scatter diagram of the patients requiring the different amounts is shown in Fig. 13,*A* and *B*.

There were four patients in whom rapid auricular fibrillation was attributed to hyperthyroidism (Cases 23, 24, 25, and 26, Table I). It was found that larger amounts of digitoxin were required to slow the rate than in patients not suffering from this disease. Symptoms of digitalis intoxication, even after large doses of the drug had been given, did not occur. In three patients it was found impossible to slow the heart rate below 80 per minute, even when doses of 3.0 mg. or more were given in from four to eight days. In every case specific therapy for the thyrotoxicosis was withheld until observation on digitalization had been completed. The difficulty encountered in slowing the rapid heart rate of hyperthyroidism with digitoxin is similar to our experience with the whole leaf.

DISCUSSION

The subjects selected for this study were thought to form a representative cross-section of cardiac patients who need digitalis. It appears that 2.06 mg. was the average dose of digitoxin required to achieve full adequate therapeutic digitalization. In only one patient was 1.2 mg., given intravenously, sufficient. The amount that we have found necessary is in close agreement with the average amount of 2.2 mg. found by De Graff.[9]

From this experience it is apparent that digitoxin when given in adequate amounts slows the ventricular rate in auricular fibrillation as effectively as the whole leaf and brings about improvement in the patient's condition which is expected from digitalis. It is our impression, however, (1) that in order to achieve adequate slowing of the ventricular rate larger amounts are required than were expected from comparison with the experience with the whole leaf, and (2) that nausea and vomiting occur more frequently than we have been accustomed to see from the whole leaf. Whether patients can be supervised on maintenance amounts of digitoxin as easily as on the whole leaf over long periods of time is now being analyzed.

Furthermore, our observations indicate that the dose of 1.2 mg. was inadequate in most instances whether it was given intravenously or orally and whether in a single initial dose or in divided doses during the first twenty-four hours. In our experience, division of the doses in the twenty-four hours of digitalization did not increase the amount of the drug required to achieve digitalization. We digitalized certain patients in twenty-four hours by giving 1.2 or 1.8 mg. in one dose followed in each case by enough drug to achieve slowing to the desired rate. The average in these was 2.1 milligrams. In other patients the amount of the drug given in twenty-four hours by this procedure was inadequate and additional amounts had to be given for some days following. When allowance was made for maintenance over these additional days and subtracted from the total amount given the patient in that time, the amount which would have digitalized the patient if given in twenty-four hours was obtained. The average amount for the

patient digitalized in this fashion also turned out to be 2.1 mg., a very close agreement with the amount required when the drug was given over a shorter time.

Although large amounts of the drug were given in this series of patients in one single dose in order to arrive at the digitalizing amount in twenty-four hours, this procedure is not recommended for general use. It appears safe in many instances to give 1.2 mg. intravenously or orally in a single dose if it is urgent and the patient has not had digitalis in two weeks, but it is safe only because it is, in most patients, far short of the total amount eventually required for full therapeutic digitalization. If digitoxin is selected when digitalization is to be accomplished in twenty-four hours in a patient at bed rest, it may be given by mouth as follows: 0.8 mg., followed in four hours by 0.5 mg., and by 0.3 mg. four hours later still, and 0.2 mg. four hours later, and then 0.2 mg. four hours later still, if necessary; the doses after the first are not to be given if the ventricular rate slows to 75 per minute or if nausea or vomiting occurs.

The patients in this study had adequate control periods before the drug was given. It was withheld until the ventricular rate became stationary or until a rising ventricular rate indicated that the patient should not be deprived longer of the drug. The drug was given as it would be used clinically and the results are those which are encountered in clinical experience.

The maintenance amounts in our series ranged from 0.1 mg. every two days to 0.2 mg. every day, the greatest number requiring between 0.1 and 0.2 mg., namely, 0.1 alternating with 0.2 mg. on successive days. This is shown in Fig. 13,*C* which reproduces a frequency diagram of the amounts of digitoxin required in these patients for maintenance, namely, to keep the ventricular rate around 70 to 75 per minute. This is similar to De Graff's[9] experience that 0.2 mg. is too much for most patients. De Graff has pointed out that the rate of dissipation of Digitaline Nativelle is slow so that toxic symptoms may last as long as one week after its discontinuance. He warns against accumulation and overdosage by the maintenance amounts. The incidence of toxic manifestations with digitoxin when additional increments are given to slow the ventricular rate to 70 per minute and to maintain the rate around this level by rationed amounts may be accounted for by the slow rate of dissipation of the drug and the long duration of its toxic effects, as Batterman and De Graff[16] have recently pointed out.

From our studies of digitalis we have ascertained the amount required to slow the ventricular rate to from 70 to 75 per minute in patients with auricular fibrillation, and we have used this amount as that which would also be the digitalizing amount in patients with normal sinus rhythm in whom the heart rate is not a guide to digitalization. This is the best yardstick available at the present time, since patients begin to improve as digitalis is absorbed and show improvement on amounts short of the full digitalizing amount.

We believe that insistence upon 1.2 mg. as the average full therapeutic digitalizing dose of digitoxin has been unfortunate since physicians have been lulled into a false sense of security at times when they have not secured the full benefits from the use of the drug. We have seen digitalis less well administered

since this recommendation entered the literature. Moreover, acceptance of a maintenance dose of 0.2 mg. daily may be hazardous since instances of toxic effect after some months of such usage are now coming to light.

CONCLUSIONS

1. In most patients 1.2 mg. of digitoxin is insufficient to achieve adequate digitalization when given either intravenously or orally.

2. The average amount of digitoxin required for adequate digitalization in this series was around 2.0 mg. if given in twenty-four hours.

3. It makes no apparent difference in the total amount required for adequate digitalization within twenty-four hours whether the drug is given in one single dose or in divided doses.

4. When adequate slowing of the heart is attained, nausea and vomiting, in our experience, occur more frequently with digitoxin than with the whole leaf.

5. The average maintenance amount of digitoxin is between 0.1 and 0.2 mg.; 0.2 mg. is too much in most patients who have been adequately digitalized.

6. In our experience it is more difficult to keep patients in equilibrium by maintenance doses of digitoxin than with the whole leaf.

7. Although large amounts of the drug in a single dose were given in this series of patients in order to arrive at the digitalizing amount in twenty-four hours, this procedure is not recommended for general use.

8. Since the method of digitalization with divided doses of digitoxin, as recommended, is effective in patients with auricular fibrillation, the same system of dosage can be transferred to patients with normal rhythm in whom the heart rate does not serve as a guide.

9. In hyperthyroidism with auricular fibrillation, larger amounts of digitoxin are required to achieve slowing of the ventricular rate than in patients with normal basal metabolic rates, an experience which is similar to that observed when the whole leaf is used.

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CONTINUOUS OBSERVATIONS OF THE ARTERIAL OXYGEN SATURATION AT REST AND DURING EXERCISE IN CONGENITAL HEART DISEASE

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ROCHESTER, MINN.

RECENT developments in the measurement of arterial oxygen saturation in man have made continuous observations practical.[5] Application of these methods makes possible a more thorough study of the arterial oxygen saturation under a variety of conditions. It is the purpose of this paper to report on a series of continuous observations of the arterial oxygen saturation in a group of patients with congenital cardiac defects.

METHODS

The C. M. R. Model 13 compensated circuit oximeter was used in all of the observations to be reported. This instrument, described by Millikan[5] in 1942, is essentially a photoelectric colorimeter designed to measure continuously and painlessly arterial oxygen saturation in the intact human ear. The earpiece of the oximeter, which weighs approximately 30 grams, is designed to be clamped to the pinna of the ear so that it is easily possible to record arterial oxygen saturation during performance of standard exercise tests or other types of activity.

The galvanometer of the instrument can be read visually and the deflections can be recorded intermittently or the galvanometer deflections can be recorded continuously with a kymographic camera. A comparison of records made simultaneously on the same subject (Fig. 1) indicates that the intermittent observations of the arterial oxygen saturation can be made with sufficient rapidity to follow accurately the changes in saturation that may occur. We have used the intermittent type of observation (readings taken and recorded every fifteen to thirty seconds) almost exclusively because of its simplicity.

Millikan[6] reported that the range of differences between oximeter saturation readings and Van Slyke analyses of simultaneous arterial blood samples was ±5 percentage points of saturation in the saturation range from 75 to 90 per cent

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and ±8 percentage points in the saturation range from 50 to 75 per cent. The instrument was reported to indicate changes in arterial oxygen saturation with substantially greater accuracy than absolute values of saturation. Baldes and co-workers[1] in 1942, Boothby and Robinson[2] and Power and co-workers[9] in 1943, and Hemingway and Taylor[4] in 1944 obtained an accuracy similar to that reported by Millikan. One of us (G. E. M.),[7] during nearly 400 calibrations of oximeter readings against analyses (Van Slyke) of simultaneously drawn arterial blood, found that the average difference between the oximeter reading and the Van Slyke value was +4.5 percentage points in the saturation range from 50 to 91 per cent. The average deviation from Van Slyke analyses was significantly different when different earpieces were used, ranging from +2.1 to +13.1 percentage points for the six earpieces tested.

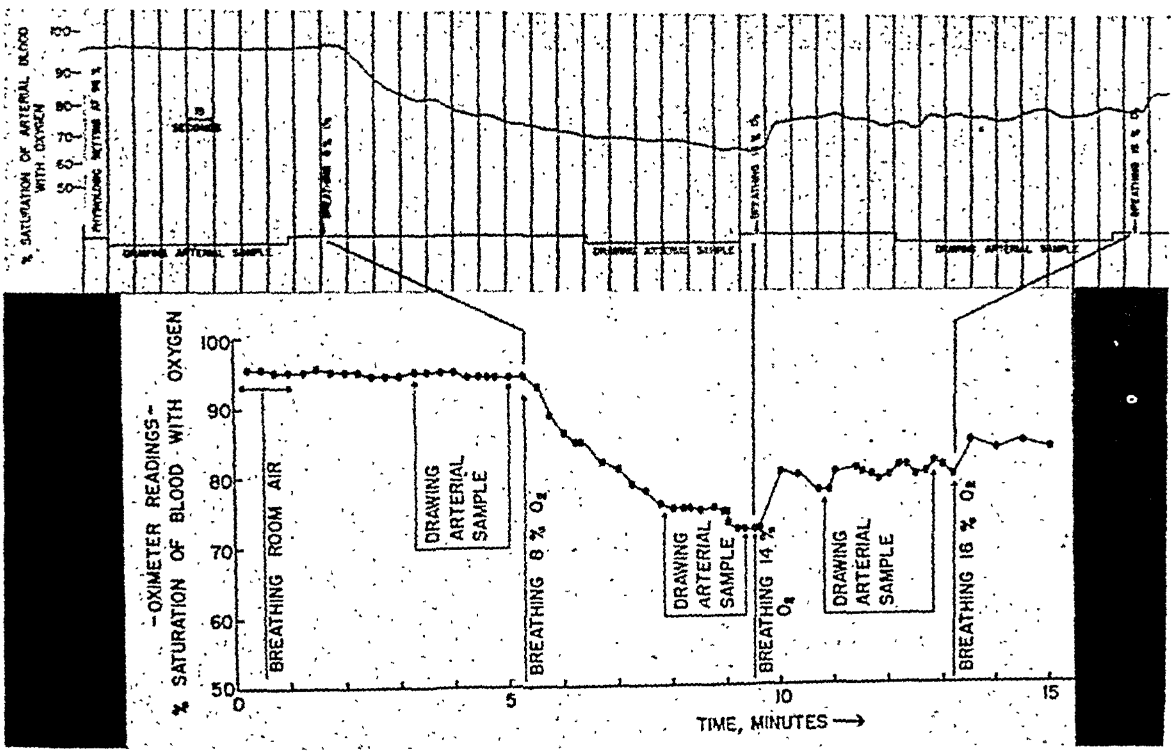

Fig. 1.—A comparison of continuous (top) and intermittent (bottom) recording of arterial oxygen saturation by means of the Millikan oximeter. These records were made simultaneously from the two ears of the same subject.

The method of collecting the data reported herein was as follows: While the patient was supine, the oximeter earpiece, already warmed up by having been turned on ten minutes earlier, was affixed to an ear. After the ear had become fully flushed (five to fifteen minutes were usually required) a clinical estimate of the patient's arterial oxygen saturation was made and the oximeter was then manually adjusted to correspond with this estimated value. Oximeter saturation readings were made and recorded every fifteen to thirty seconds from this point on. A radial arterial puncture was done under local procaine hydrochloride anesthesia shortly after the observation period was started. The oximeter reading was carefully noted at the time this sample was being drawn. In some of the tests an indwelling needle was placed in the radial artery so that

additional arterial samples could be obtained at will during the periods of exercise and recovery.

The arterial blood samples were collected under a minimal amount of mineral oil containing a small quantity of powdered heparin as an anticoagulant. A small amount of clean mercury was aspirated into the syringe, after the blood was drawn, to act as a mixing bead. The sample was tightly capped and stored in an ice bath in the dark until it was analyzed. Within an hour after the sample was drawn, analyses were carried out for oxygen content and oxygen capacity by the Van Slyke manometric method[8] as described by Roughton and co-workers.[10]

Each patient, while supine, was given 100 per cent oxygen to breathe by means of a United States Air Forces A-15 oxygen mask, the flow being controlled by means of an oxygen pressure demand regulator, United States Air Forces Type A-16. The magnitude of the increase of the oximeter saturation reading and the time required to attain the maximal value were noted. After the patient's arterial saturation had stabilized while he was breathing oxygen, the gas was then administered under a positive pressure of from two to four inches (5 to 10 cm.) of water (by means of the A-16 regulator) and the effect on the oximeter saturation reading was noted. The patient was then allowed to breathe room air again and the time required for the oximeter saturation reading to return to the original value was recorded. Next the patient stood up and remained standing quietly at the bedside until the saturation level became stable. He then began walking on a treadmill at 1.7 miles per hour. The patient was exercised on the treadmill for a maximum of five minutes. The exercise test was terminated earlier if the patient developed severe respiratory or circulatory distress. The patient reclined immediately after the exercise test and was observed until he had regained the original resting saturation value.

After all of the oximeter observations on the patient had been completed, each oximeter reading was corrected by addition, or subtraction, of the amount of the difference that was present between the initial resting per cent saturation value determined by Van Slyke analysis of the arterial blood and the average actual oximeter saturation reading during the period that the arterial sample was being drawn. The magnitude of the theoretical error resulting from the thus unavoidably introduced error in the initial adjustment of the oximeter saturation reading has been calculated.* The difference between the decrease in arterial

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*Equation for calculation of the theoretical change in arterial saturation from the change in arterial saturation indicated by the oximeter when the initial adjustment of the saturation reading of the instrument has been incorrectly made is $S_x = \frac{(BT_1 + S_0)\ (BT_2 + S_2)}{(BT_1 + S_1)} - (BT_2)$, in which B represents bias ratio setting of oximeter; T_1, initial ear thickness reading in millimeters†; T_2, final ear thickness reading in millimeters†; S_0, correct initial saturation reading in millimeters† (from Van Slyke analysis of arterial blood); S_1, initial saturation reading in millimeters (as instrumentally adjusted by operator); S_2, final saturation reading in millimeters†; and S_x,‡ final saturation reading in millimeters† if initial instrumental adjustment had been correct.

†Galvanometer deflection in millimeters above 50 per cent saturation on the galvanometer scale.

‡Millimeter "saturation readings" can be converted to percentage saturation by the following equation: $P = 100\ \left(1 - e^{-\frac{S}{1.444K}}\right) + 50$, in which S represents the saturation reading in millimeters†; K, the number of millimeters between 50 per cent and 100 per cent saturation on the oximeter scale; and e equals 2.718.

These equations were derived by R. E. Jones, B.E.E., Consulting Engineer, Mayo Clinic.

oxygen saturation produced by exercise as read on the oximeter and the theoretical decrease in saturation which would have been indicated by the oximeter if the initial setting had been correct ranged from −2 to +3 percentage points, the average being +0.7 per cent saturation (Table I). It is of practical interest that the magnitude of the theoretical errors in oximeter readings when the instrument is used in this manner is less than the inherent error which has been reported for the instrument.

TABLE I. THE CALCULATED THEORETICAL ERRORS IN THE CHANGES IN ARTERIAL SATURATION INDICATED BY THE OXIMETER WHICH RESULT FROM THE DISPLACEMENT OF THE OXIMETER SCALE AND WHICH ARE INTRODUCED WHEN THE INSTRUMENT IS INITIALLY ADJUSTED TO INDICATE A SATURATION VALUE BASED ON A CLINICAL ESTIMATE OF THE DEGREE OF CYANOSIS

PATIENT	INSTRUMENTAL SETTING OF OXIMETER AT REST (%)*	ARTERIAL SATURATION AT REST, VAN SLYKE ANALYSIS (%)*	OXIMETER READING DURING EXERCISE (%)*	INDICATED DECREASE IN ARTERIAL O_2 SATURATION (OXIMETER) (%)*	CALCULATED INDICATED DECREASE IN ARTERIAL O_2 SATURATION IF OXIMETER HAD BEEN CORRECTLY SET AT REST† (%)*	THEORETICAL ERROR IN OXIMETER READING DUE TO INCORRECT INSTRUMENTAL SETTING (%)*
				"A"	"B"	"B" − "A"
1	83	87	71.0	12.0	11.0	+1
2	77	79	61.5	15.5	15.5	0
3	73	53	52.0	21.0	18.0	+3
4	75	45	64.0	11.0	8.0	+3
5	91	81	85.5	5.5	5.5	0
6	90	79	83.0	7.0	6.5	+0.5
8	73	79	45.0	28.0	29.5	−1.5
9	75	91	66.5	8.5	10.5	−2.0
10	74	67	56.0	18.0	16.0	+2.0
11	80	79	68.0	12.0	11.5	+0.5
12	73	67	62.0	11.0	10.5	+0.5
14	80	68	73.5	6.5	5.5	+1.0
15	73	71	59.0	14.0	13.5	+0.5
Mean	78.2	72.8	65.2	13.1	12.4	+0.7

*Per cent arterial oxygen saturation.
†Data calculated from the equation given in the footnote on p. 670.

RESULTS

The data presented in this paper were obtained during studies conducted on twenty patients seen at the Mayo Clinic between September, 1946, and May, 1947. Fifteen of these patients had a cyanotic type of congenital cardiac defect. The fifteen cases included the tetralogy of Fallot, Eisenmenger complex, and interventricular and interatrial septal defects with right to left shunts. The ages of these fifteen patients ranged from 3½ to 30 years. Nineteen students, technicians, and doctors, whose ages ranged from 9 to 60 years, were used as

normal controls in this study. The results obtained from these two groups are presented in Table II.

The responses of the arterial oxygen saturation of the group of normal subjects to the various conditions imposed on them were remarkably uniform. There was no significant difference in the responses of the two sexes or of different age groups. When the normal individuals under ordinary resting conditions were given pure oxygen to breathe, their oximeter saturation readings increased from 1 to 5 percentage points (mean increase, 2.7 percentage points), substantiating Boothby and Robinson's findings. These results indicate that the arterial oxygen saturation of normal subjects ranges from 95 to 99 per cent (mean, 97.3 per cent) at the altitude of 1,000 feet where these measurements were made. This normal group attained oximeter saturation readings of 100 per cent in from 0.5 to 3.0 minutes (mean, 1.3 minutes) after they started breathing pure oxygen. These times are slightly longer than those reported by Fowler and Comroe.[3] Giving the oxygen under positive pressure up to four inches (10 cm.) of water caused no further increase in their arterial oxygen saturation. When individuals of the normal group stood upright (from a supine position) and when they walked on the treadmill for five minutes at 1.7 miles per hour, there was no significant change in their arterial oxygen saturation.

The average resting arterial oxygen saturation of the cyanotic patients was 71 per cent (range, 45 to 91 per cent), while in normal subjects, the saturation was found to be 98 per cent. The mean erythrocyte count of the cyanotic individuals was 6,480,000 per cubic millimeter and their hematocrit values averaged 70 per cent (Table III). This group of patients gave responses widely different from those of the normal individuals. Breathing pure oxygen produced an increase in oximeter saturation reading of from 2.0 to 16.5 percentage points (mean, 6.2 percentage points). The time required to attain the maximal saturation reading when 100 per cent oxygen was breathed ranged from 1.0 to 6.0 minutes (mean, 3.0 minutes). When pure oxygen was administered to these cyanotic patients, under positive pressure, oximeter saturation readings increased, on the average, 1.6 percentage points over the saturation values attained with pure oxygen administered with no positive pressure.

The individuals in the cyanotic group had changes in oximeter saturation readings ranging from +3.0 to −10.0 percentage points (mean, −2.4 percentage points) when they went from the supine to the erect position. In the cyanotic patients, walking on the treadmill at 1.7 miles per hour produced decreases in oximeter saturation readings of from −3.5 to −19.0 percentage points (mean, −10.9 percentage points). The exercise was terminated in less than 5.0 minutes in six instances because the patients were in distress or were fatigued. Four of the patients were unable to exercise longer than three minutes. Average duration of the exercise was 4.2 minutes.

Five patients who had noncyanotic types of congenital cardiac defects were studied (Table IV). Their ages ranged from 2½ to 19 years. Their lesions included atrial and ventricular septal defects and one patent ductus arteriosus. The values for the arterial oxygen saturations of these individuals obtained in

TABLE II. THE RESPONSE OF THE ARTERIAL OXYGEN SATURATION (OXIMETER READING) OF PATIENTS WITH A CYANOTIC TYPE OF CONGENITAL CARDIAC DEFECT TO VARIOUS CONDITIONS*

PATIENT		INCREASE IN OXIMETER SATURATION READING WITH 100% O_2 (%)†	TIME TO REACH MAXIMAL INCREASE (MIN.)	EFFECT OF PRESSURE‡ BREATHING WITH O_2 (%)†	TIME TO RETURN TO CONTROL VALUE (MIN.)	EFFECT OF STANDING POSTURE (%)†	DURATION OF WALK AT 1.7 M.P.H. (MIN.)	EFFECT OF WALK (%)†	TIME FROM START OF WALK TO MAXIMAL SATURATION CHANGE (MIN.)	TIME FROM END OF WALK TO CONTROL VALUE (MIN.)
1		5.5	1.0	—	2.0	−2.0	4.5	−17.0	4.5	4.0
2		7.0	2.5	+2.5	—	−3.5	5.0	−12.0	5.0	6.0
3		—	—	—	—	−5.0	1.5	−9.0	2.5	3.0
4		2.0	0.5	+3.0	2.0	+3.0	5.0	−14.0	5.0	5.5
5		16.5	4.0	0.0	4.5	0.0	5.0	−6.0	1.0	—
6		5.5	4.0	—	3.0	−6.0	3.0	−4.0	3.0	1.0
7		4.0	6.0	—	2.5	—	—	—	—	—
8		5.5	1.75	—	3.75	−10.0	5.0	−18.5	5.5	4.0
9		6.5	4.0	0.0	3.5	−1.5	5.0	−3.5	3.5	2.0
10		6.0	4.0	+5.0	1.5	−3.0	4.75	−14.0	4.75	3.0
11		6.5	3.0	+1.0	4.0	0.0	5.0	−8.5	2.5	2.5
12		3.0	1.5	—	1.5	−6.0	2.75	−6.0	2.75	2.5
13		5.0	2.0	0.0	1.0	+2.0	5.0	−13.5	3.0	7.0
14		7.0	4.0	—	2.2	−2.0	5.0	−8.0	3.2	3.0
15		6.0	3.0	—	2.0	0.0	2.75	−19.0	2.75	3.75
Mean of patients' values		6.2	3.0	+1.6	2.6	−2.4	4.2	−10.9	3.5	3.6
Values for 19 normal subjects	Mean	2.7	1.3	+0.1	2.8	0.0	5.0	−0.3	—	—
	Range	+1.0 to +5.0	+0.5 to +3.0	0.0 to +1.0	+1.0 to +5.0	−1.0 to 0	—	−2.0 to 0	—	—

*Average values obtained from normal individuals under similar conditions are given in the last line.
†Percentage points of arterial oxygen saturation.
‡A positive pressure of 2 to 4 inches (5 to 10 cm.) of water was used.

TABLE III. RESULTS OF ANALYSES OF ARTERIAL BLOOD FROM PATIENTS WITH CYANOTIC TYPES OF CONGENITAL CARDIAC DEFECTS*

PATIENT	SEX	AGE (YR.)	DIAGNOSIS	ARTERIAL O_2 CONTENT (VOL. %)	ARTERIAL O_2 CAPACITY (VOL. %)	ARTERIAL O_2 SATURATION (%)	HEMOGLOBIN† (GM. PER 100 C.C.)	ERYTHROCYTES (MILLIONS)	HEMATOCRIT (%)
1	F	5	Tetralogy	17.0	19.5	87	14.6	4.30	—
2	F	15	Indeterminate; ? tricuspid atresia	20.1	25.3	79	18.9	6.11	65
3	M	3.5	Tetralogy	13.9	26.2	53	19.6	5.34	65
4	F	13	Tetralogy and dextrocardia	15.1	33.6	45	25.1	7.31	80
5	F	16	Atrial septal defect	17.9	22.2	81	16.6	—	50
6	M	16	Cor triloculare and dextrocardia	18.3	23.2	79	17.3	4.51	55
7	M	7	Tetralogy	18.4	29.0	63	21.6	8.27	89
8	M	5	Tetralogy	25.5	32.4	79	24.2	8.02	84
9	M	30	*Eisenmenger complex*	22.5	24.7	91	18.4	5.32	60
10	F	8	Tetralogy	21.7	32.2	67	24.0	7.95	80
11	F	14	Atypical tetralogy	17.7	22.3	79	16.6	4.12	52
12	M	4	Tetralogy	18.7	28.1	67	21.0	8.13	86
13	M	16	Tetralogy	—	—	—	—	6.45	63
14	M	8	Tetralogy	22.5	33.2	68	24.8	7.54	78
15	F	7.5	Tetralogy	20.9	29.4	71	21.9	7.41	74
Mean values for patients				19.3	27.2	71	20.3	6.48	70
Mean values for 19 normal subjects				19.7	20.1	98	15.0	4.75‡	50‡

*Mean values for normal subjects are included in the last line of the table.

†Hemoglobin concentration was calculated from the oxygen capacity of the blood (volumes per cent capacity ÷ 1.34 = grams of hemoglobin per 100 c.c. of blood).

‡Analyses of venous blood samples were made by the hematology laboratories of the Mayo Clinic.

TABLE IV. RESULTS OF ANALYSES OF ARTERIAL BLOOD FROM PATIENTS WITH NONCYANOTIC TYPES OF CONGENITAL CARDIAC DEFECTS

PATIENT	SEX	AGE (YR.)	DIAGNOSIS	ARTERIAL OXYGEN CONTENT (VOL. %)	ARTERIAL OXYGEN CAPACITY (VOL. %)	ARTERIAL OXYGEN SATURATION (%)	HEMOGLOBIN, GM. PER 100 C.C. (CALCULATED FROM O_2 CAPACITY)	ERYTHROCYTES (MILLIONS)
16	M	16	Interatrial septal defect	19.1	19.5	98	14.6	—
17	F	5	Interventricular septal defect	14.9	15.4	97	11.5	4.27
18	F	19	Atrial and ventricular septal defects	15.7	16.7	94	12.5	—
19	F	2.5	Patent ductus arteriosus	15.1	16.7	90	12.5	4.69
20	F	5	Interauricular septal defect	17.9	19.4	92	14.5	4.68
Mean		9.5		16.5	17.5	94	13.1	4.55

TABLE V. THE RESPONSES OF THE ARTERIAL OXYGEN SATURATION (OXIMETER READING) OF PATIENTS WITH NONCYANOTIC TYPES OF CONGENITAL CARDIAC DEFECTS TO VARIOUS CONDITIONS

PATIENT	INCREASE IN OXIMETER SATURATION READING WITH 100% O_2 (%)*	TIME TO REACH MAXIMAL INCREASE (MIN.)	EFFECT OF PRESSURE† BREATHING WITH O_2 (%)*	TIME TO RETURN TO CONTROL VALUE (MIN.)	EFFECT OF STANDING POSTURE (%)*	DURATION OF WALK AT 1.7 M.P.H. (MIN.)	EFFECT OF WALK (%)*	TIME FROM START OF WALK TO MAXIMAL SATURATION CHANGE (MIN.)	TIME FROM END OF WALK TO CONTROL VALUE (MIN.)
16	4.0	1.0	0.0	1.5	0.0	5.0	−2.0	0.5	0.5
17	—	—	—	—	0.0	5.0	0.0	—	—
18	3.0	3.0	0.0	3.0	−4.0	5.0	−1.0	1.5	2.5
19	—	—	—	—	+2.0	3.0	−3.5	3.0	—
20	5.0	1.0	+0.5	2.0	0.0	5.0	−3.0	1.0	2.0
Mean	4.0	1.7	+0.2	2.2	−0.4	4.6	−1.9	1.5	1.7

*Percentage points of arterial oxygen saturation.
†A positive pressure of 2 to 4 inches (5 to 10 cm.) of water was used.

TABLE VI. COMPARISON OF OXIMETER SATURATION READINGS WITH ARTERIAL OXYGEN SATURATION VALUES DETERMINED BY VAN SLYKE ANALYSES OF SIMULTANEOUSLY DRAWN ARTERIAL BLOOD AT REST AND DURING EXERCISE

PATIENT	HEMOGLOBIN (GM. PER 100 C.C.)	OXIMETER READING AT REST (%)*	OXIMETER READING DURING EXERCISE (%)*	OXIMETER CHANGE DURING EXERCISE (%)*	ARTERIAL SATURATION AT REST (VAN SLYKE) (%)*	ARTERIAL SATURATION DURING EXERCISE (VAN SLYKE) (%)*	SATURATION CHANGE DURING EXERCISE (VAN SLYKE) (%)*	DIFFERENCE IN RECORDED CHANGE (VAN SLYKE AND OXIMETER) (%)*
21	25.2	67	57	−10	86	69	−17	− 7
22	26.2	53	46	− 7	58	44	−14	− 7
23	11.9	90	70	−20	86	53	−33	−13
24	12.2	90	89	− 1	96	98	+ 2	+ 3
25	25.4	63	48	−15	81	45	−36	−21
Mean	20.2	72.6	62	−10.6	81.4	61.8	−19.6	− 9.0

*Percentage saturation of blood with oxygen.

response to the various tests (Table V) lay between those obtained from the normal group and those obtained from the cyanotic group.

Inasmuch as the scale of the oximeter is calibrated to read only from 50 to 100 per cent saturation, and since some cyanotic patients have resting arterial oxygen saturations of less than 50 per cent, a further effort was made to determine if the instrument gives reliable measurements of the saturation changes occurring in these very low ranges. Arterial blood samples were taken before and during exercise on five patients, four of whom had arterial oxygen saturation values that were markedly changed by exercise. The arterial oxygen saturation as determined by Van Slyke analyses of these blood samples has been compared with simultaneous oximeter readings (Table VI). In these instances, the change in arterial saturation during exercise, as indicated by the oximeter, differed by +3 to −21 percentage points from the change in arterial saturation found by Van Slyke analyses of the arterial blood. The average difference was −9.0 percentage points.

COMMENT

The use of the oximeter in studying patients with congenital heart disease offers several advantages. Continuous observation of the arterial oxygen saturation is possible. True values of the resting arterial oxygen saturation can thus be estimated if one waits until the patient is resting comfortably before making the instrumental saturation reading and then notes carefully the changes in saturation which may occur during the period of the arterial puncture. Fig. 2 gives an example of the marked decrease in the oximeter saturation reading which may occur in an infant as a result of crying and struggling when an arterial puncture is done. A patient's response to standardized procedures, such as exercising or breathing 100 per cent oxygen, may be studied continuously with ease. Pre- and postoperative studies made with an oximeter (Figs. 3 and 4) may be of much more significance and may give more information than a single arterial oxygen analysis done before and after surgical intervention.

The chief disadvantage of the oximeter in studies on cyanotic patients is the large range of error inherent in the instrument in the lower ranges of arterial saturation. The relatively large discrepancies found between oximeter readings during exercise and analysis of simultaneous arterial samples obtained in four cyanotic, polycythemic patients may indicate that the range of error is greater in patients of this type than it is in normal subjects rendered anoxic by exposure to high altitude or to low-oxygen, high-nitrogen mixtures.

Since the oximeter measures only *changes* in the arterial oxygen saturation, it is necessary to make a "setting" of the instrument at some value before observations are started. When it is used on normal subjects, an initial "physiologic setting" of the instrument to read 98 per cent saturation (subject breathing room air) is made and all subsequent saturation changes are measured from this point. However, when one is using the oximeter on individuals whose arterial oxygen saturation may not be normal, one is no longer justified in making such an arbitrary "physiologic setting" of the instrument but must do an arterial puncture and Van Slyke analysis for oxygen at some time during the course of the observa-

tions to establish a reference point for all of the readings made before and after the arterial puncture. This correction of the oximeter readings is somewhat inconvenient but is necessary to relate instrumental readings to actual arterial saturation values. It is of practical convenience that, theoretically, the oximeter records changes in arterial saturation with only relatively small errors in spite of considerable displacement of the saturation scale which may result when initial instrumental settings are made without a knowledge of the actual arterial saturation level, as is often the case when one is dealing with cyanotic patients. However, it should be kept in mind that even at best the range of error in oximeter readings is relatively large. This range of error may be even greater when one is dealing with patients with varying degrees of polycythemia, abnormal skin pigmentation, and so forth (Table VI).

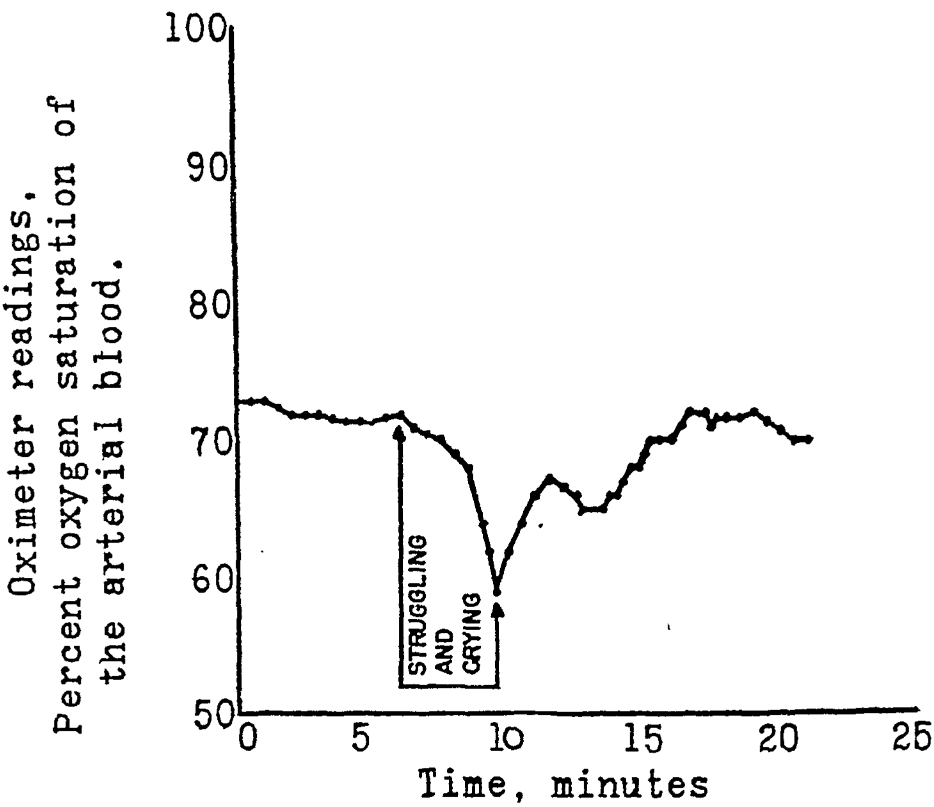

Fig. 2.—The effect of the crying and struggling associated with an arterial puncture on the arterial oxygen saturation. The patient was 13 years old. The diagnosis was cyanotic congenital heart disease.

An occasional shortcoming of the oximeter occurs when a patient is encountered whose ears are too small to accommodate the present earpieces. This condition occurs frequently in infants and women and prohibits oximeter studies on these individuals. Also, some Negroes and others with a very heavily pigmented

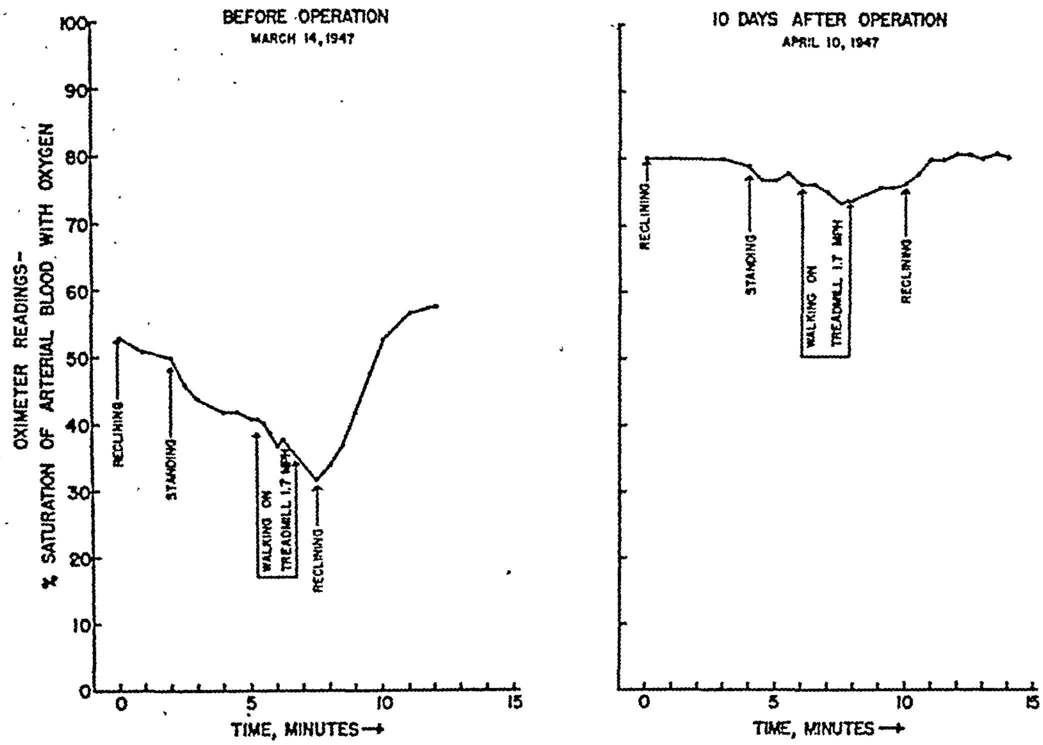

Fig. 3.—The effect of the Blalock operation on the arterial oxygen saturation at rest and during exercise in Patient 3, 3½ years of age. The diagnosis was the tetralogy of Fallot. Ten days after the operation the resting arterial oxygen saturation was increased 28 percentage points, and the magnitude of the decrease of the arterial oxygen saturation produced by exercise was reduced from 20 to 7 percentage points.

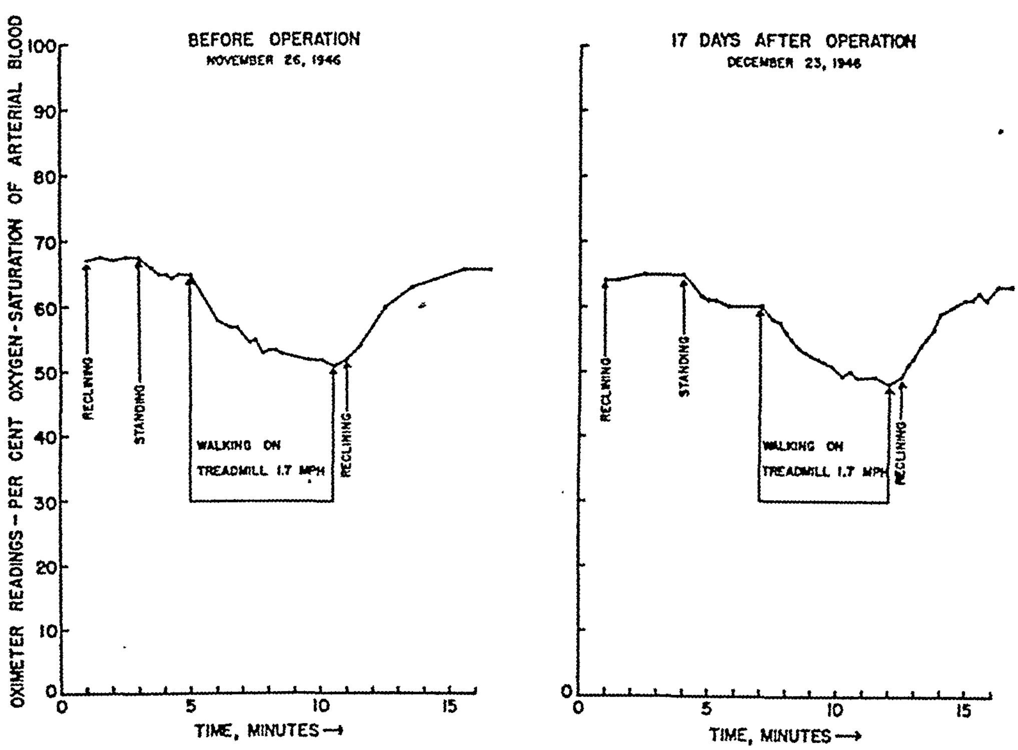

Fig. 4.—A comparison of the arterial oxygen saturation at rest and during exercise before and after a Blalock type operation in which the anastomosis was not satisfactory. This result was secured in Patient 10, 8 years of age. The diagnosis was the tetralogy of Fallot. The resting arterial oxygen saturation and the response to exercise were not significantly altered by the operation.

skin may not be suitable for oximetric measurements because of the spectral transmission characteristics of their ears. It has been found that there is a relatively greater absorption of the light in the spectral region from 600 to 800 millimicrons by the colored ear than by the normal white ear. This particular spectral region activates the "red cell" of the oximeter earpiece; hence, variations in this region may critically alter the function of the oximeter. Except for the two groups of patients just mentioned, however, the oximeter finds nearly universal applicability for continuous indication of variations in arterial oxygen saturation.

The most clear-cut and significant differences in the responses of the arterial oxygen saturation of the normal subjects and of the cyanotic group of patients were seen when the positions of the patients were changed or when exercising was done. The subjects in the normal group caused practically no change in oximeter-saturation readings when they stood up (from a supine position) or when they exercised by walking on a treadmill for five minutes at 1.7 miles per hour. The individuals of the cyanotic group, however, characteristically caused a decrease (mean, 2.4 percentage points) in oximeter saturation readings when they stood upright and more severe decreases (mean, 10.9 percentage points) when they walked at 1.7 miles per hour for an average of 3.5 minutes. A walking-exercise test was chosen because it was familiar to everyone and required no training for its performance. Furthermore, it called into action the most commonly used large muscle groups of the body. Even the 3-year-old patients were able to co-operate by walking on the treadmill as desired.

The decrease in the arterial oxygen saturations of the cyanotic individuals during exercise was an indication of the inability of the heart to pump enough blood through the lungs to keep the oxygen replaced that was being lost at an accelerated rate in the muscle tissue. Thus, these responses would seem to be an index to the severity of the right to left intracardiac shunt and the proportion of blood that enters the pulmonary circulation.

In the group of patients with cyanotic heart disease it was possible to demonstrate a significant inverse correlation (correlation coefficient, −0.6) between the resting arterial oxygen saturation and the hemoglobin content of the blood. Likewise, there tended to be a correlation (correlation coefficient, +0.4) between blood hemoglobin content and the decrease in oximeter saturation reading that occurred during the exercise test (Tables II and III). These relationships are readily understood since the degree of hypoxia is one of the factors which regulate the erythrocyte and, hence, the hemoglobin content of the circulating blood.

It is of interest to note that the magnitude of the increase and the time required for these cyanotic patients to attain maximal arterial oxygen saturation when breathing pure oxygen exceeded the values obtained from normal subjects. These findings are apparently the result of the continuous mixing, in the left side of the heart, of the blood from the lungs (completely saturated and carrying approximately 2 volumes per cent of oxygen in physical solution) with mixed venous blood from the right side of the heart passing through the septal defect. Under these conditions the maximal arterial oxygen saturation increase possible and the time required to attain this maximum depend on the proportion of the

venous blood going through the lungs and passing through the shunt and on the circulation time. If the arteriovenous difference remains constant, maximal saturation of the peripheral arterial blood is approached asymptotically as successive circulations of the blood increase (but by ever-lessening amounts) the oxygen saturation of the venous blood reaching the right side of the heart.

SUMMARY

Continuous observations, made with the Millikan compensated circuit oximeter, of the arterial oxygen saturation of nineteen normal subjects and of twenty patients with cyanotic and noncyanotic types of congenital cardiac defects are presented.

When normal individuals were given pure oxygen to breathe, their arterial oxygen saturation increased, on the average, 2.7 percentage points (to reach 100 per cent saturation) in 1.3 minutes. In fifteen patients with a cyanotic type of congenital cardiac defect, breathing pure oxygen produced an average increase in oximeter saturation reading of 6.2 percentage points attained in an average period of 3.0 minutes.

Normal subjects showed practically no change in their arterial oxygen saturation when they changed from the supine to the erect position or when they walked on a treadmill for five minutes at 1.7 miles per hour. Patients with a cyanotic type of congenital cardiac defect showed an average decrease in oximeter saturation reading of 2.4 percentage points when they stood up and 10.9 percentage points when they exercised on the treadmill.

It is suggested that the compensated circuit oximeter is of considerable value in studying patients with congenital cardiac defects for two reasons: (1) Its use in conjunction with Van Slyke analyses of arterial blood makes possible a more accurate estimation of the resting arterial oxygen saturation of such patients. (2) Measurements of the arterial oxygen saturation can be made continuously during the performance of various cardiovascular and respiratory function tests, thus greatly facilitating an objective interpretation of the results obtained. Such tests serve as a valuable adjunct in the judging of the efficacy of corrective surgical procedures in these patients.

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CORONARY ARTERY DISEASE IN MEN EIGHTEEN TO THIRTY-NINE YEARS OF AGE

REPORT OF EIGHT HUNDRED SIXTY-SIX CASES, FOUR HUNDRED FIFTY WITH NECROPSY EXAMINATION*

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(*Continued from page 526*)

PATHOLOGIC DATA

The protocols of the 450 patients who died varied greatly in detail and accuracy, since the necropsies were performed all over the world and by many different individuals. The hearts from only twenty were available to the Army Institute of Pathology, but blocks of tissue, paraffin blocks, and slides were contributed in practically all cases, and these were carefully studied, additional sections being made and special stains being used when desirable. Tissues of sections of the myocardium and of one or more of the larger coronary arteries were available in most cases.

Size of the Hearts.—The weights of 374 of the hearts were recorded. Since no comment was made regarding the size of the other seventy-six hearts, it may safely be assumed that practically all of them appeared to the prosectors to be of normal size. In arriving at the degree of hypertrophy of the hearts, the tables of normal weights of hearts correlated with body weight, as prepared by H. L. Smith[142] in 1928, were used as the starting point. Then the following heart weights were arbitrarily devised.

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DEGREE OF HYPERTROPHY OF HEARTS

GRADE	GRAMS IN EXCESS OF AVERAGE
0	49
0+	50 to 74
1	75 to 112
1+	113 to 149
2	150 to 187
2+	188 to 224
3	225 to 262
3+	263 to 299
4	300 to 375
4+	Over 376

Thus, if a heart weighed 573 grams instead of the 323 grams which would be normal according to Smith's table, hypertrophy would be considered to be Grade 3 on the basis of these criteria.

Table XXVIII shows the degree of hypertrophy observed in the 450 cases. According to this listing, 232 (52 per cent) of the hearts of those patients were hypertrophied to some extent, and seventy (16 per cent) were hypertrophic, from Grade 2 to Grade 4+. Inasmuch as there were very few cases of hypertension in the whole series (not more than fifteen or sixteen patients were known to have hypertension at the time of death, eight of whom were only slightly hypertensive, and only six of whom had valvular disease that might have caused hypertrophy), these figures are arresting. In 205 cases roentgenograms of the chest at induction showed the cardiac shadows of all patients to be within normal limits.

TABLE XXVIII. CARDIAC HYPERTROPHY IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE

GRADE OF HYPERTROPHY*	NO.	%
None or probably none†	218	48.4
0+	40	8.9
1	78	17.3
1+	44	9.8
2	30	6.7
2+	11	2.4
3	9	2.0
3+	8	1.8
4	9	2.0
4+	3	0.7
Total	450	100.0

*Degree of hypertrophy based on tables of normal weights of hearts correlated with body weight, as prepared by Smith.[142]

†In 76 cases the weights were not stated. In some the prosectors stated that the hearts were not enlarged. It is assumed that in the others, the prosectors considered that the hearts were not enlarged.

Correlation of Cardiac Hypertrophy With Various Factors.—There was no indication that cardiac hypertrophy is correlated with induction blood pressure, but the series provides too few cases to study this relationship very closely.

There was a previous history of cardiac disease, either definite or possible, in 34 per cent of the patients with hypertrophy of Grade 2 and over, as compared with 17 per cent of those with no hypertrophy or hypertrophy less than Grade 2.

There was a significantly high correlation between cardiac hypertrophy and the duration of the terminal illness. In only 11 per cent of the patients in whom the terminal illness lasted less than twenty-four hours was there cardiac hypertrophy of Grade 2 or more, whereas it was found in 33 per cent of the patients in whom the terminal illness lasted more than twenty-four hours. Similarly, 42 per cent of the men who had hypertrophy of Grade 2 or more lived longer than twenty-four hours, as compared with only 12 per cent of the men with no hypertrophy or hypertrophy less than Grade 2. These figures may indicate that hypertrophy is the result of a compensating mechanism which makes the heart somewhat better able to cope with insult.

There was found to be no significant difference in the proportion of patients with sclerotic occlusion among those with no cardiac hypertrophy or hypertrophy under Grade 2 and those with cardiac hypertrophy of Grade 2 or over. About one-half of the patients in each group had sclerotic occlusion somewhere in the left anterior descending artery, the left circumflex artery, or the right circumflex artery.

There was no significant difference in the proportion of patients in whom there was thrombotic occlusion among those with no cardiac hypertrophy or hypertrophy under Grade 2 and those with hypertrophy of Grade 2 and over. About one-half of the men in each group had thrombotic occlusion in one of the major coronary arteries.

The occurrence of myocardial infarcts, however, was definitely correlated with cardiac hypertrophy, since gross infarcts were found more than twice as frequently with cardiac hypertrophy of Grade 2 and over as when there was no cardiac hypertrophy or hypertrophy under Grade 2 (Table XXIX). Likewise,

TABLE XXIX. CARDIAC SIZE IN RELATION TO MYOCARDIAL INFARCTS AMONG MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE

INFARCTS	DEGREE OF HYPERTROPHY			
	NORMAL SIZE OR HYPERTROPHY UNDER GRADE 2*		HYPERTROPHY GRADE 2 AND OVER	
	NO.	%	NO.	%
None	283	74.5	32	45.7
Gross	77	20.2	35	50.0
Microscopic	20	5.3	3	4.3
Total	380	100.0	70	100.0

*There were 76 hearts, the weights of which were not recorded, which were probably not appreciably enlarged.

myocardial scarring was more common in the group of patients with cardiac hypertrophy of Grade 2 and over than in the other group; the ratio was 72 to 55 per cent (Table XXX). There was also a significantly greater proportion of patients with mural thrombi among those with cardiac hypertrophy of Grade 2 and over than among those of the other group (21 per cent as against 8 per cent).

TABLE XXX. CARDIAC SIZE IN RELATION TO MYOCARDIAL SCARRING IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE

SCARRING	SIZE OF HEART					
	NORMAL SIZE OR HYPERTROPHY UNDER GRADE 2		HYPERTROPHY GRADE 2 AND OVER		HYPERTROPHY NOT STATED*	
	NO.	%	NO.	%	NO.	%
None	133	43.9	20	28.2	27	35.5
Diffuse	105	34.6	26	36.6	24	31.6
Focal	49	16.2	20	28.2	20	26.3
Diffuse and focal	10	3.3	5	7.0	2	2.6
Not stated	6	2.0	0	0.0	3	4.0
Total	303	100.0	71	100.0	76	100.0

*Probably little or none.

In four patients with old rheumatic valvulitis and in the one patient with syphilitic aortitis, there was hypertrophy of Grade 2 + to 4.

Vascular lesions in the kidneys did not influence the factor of cardiac hypertrophy, since the two findings were present in about the same percentage in each of the two groups (under Grade 2 and Grade 2 and over).

These facts tend to clarify the old controversy of whether coronary artery sclerosis or myocardial degeneration influences hypertrophy of the heart. There is a definite indication that myocardial degeneration does cause hypertrophy, since the hearts more seriously damaged by infarction or scarring and those with mural thrombi tended to be larger than those without these lesions but with coronary artery disease alone. The true explanation of this result is debatable. However, it may be that there is in the early stage of the disease a relative myocardial anoxia which reduces the tone of the myocardium and allows stretching of the fibers. Additional stretching would be likely to occur with each acute occlusion of one of the coronary arteries. Gradually, however, the collateral circulation might be built up in certain cases to the point where hypertrophy of myocardial fibers could occur.

When the literature is reviewed with reference to the question of coronary artery disease causing hypertrophy, one finds that criteria for hypertrophy are rarely given or that any weight over a certain number of grams is assumed to indicate hypertrophy, and that the presence or absence of hypertension as a factor is usually not clearly stated. The following are outstanding examples. Among Nathanson's[34] 113 cases, hearts weighing more than 400 grams were

considered to be enlarged, and in sixty-eight cases the hearts weighed more than that. Congestive failure was more common with large hearts (forty-six cases). Barnes and Ball[22] stated that in a series of forty-nine cases of infarction, the hearts tended to exceed average weights. Among 100 autopsied cases Lisa and Ring[45] found the average weight to be 519 grams, with a range of 200 to 925 grams; the cause of the hypertrophy was not apparent. Appelbaum and Nicholson[54] reported the heart weight in ninety-four of 150 cases and stated that the majority of hearts were above the average range; sixty-nine had weights greater than 400 grams. However, many patients had had hypertension, and the authors concluded that factors other than coronary artery sclerosis were responsible for the hypertrophy. Glendy and co-workers[62] studied a series of 100 patients under 40 years of age and 300 over 80 years of age. Of the 100 younger patients, 37 per cent had enlarged hearts. The authors stated that considerably more of the younger group had hearts of normal size. In a series of forty-eight cases, Woods and Barnes[143] found forty-five hearts to be enlarged, the average weight being 496 grams. These authors considered the average normal weight to be 330 grams. Bruenn and associates[92] found hypertrophy of the heart to exist in 236 (70 per cent) of 338 cases, the average weight being 543 grams. In Bean's[14] series of 300 cases hypertrophy was found in 84 per cent; hearts weighing more than 350 grams in women and 400 grams in men were considered to be hypertrophied. Bean concluded that the "majority of cases with cardiac infarction have enlarged hearts." In 1928 Parkinson and Bedford[40] concluded that "coronary artery disease alone can cause some degree of hypertrophy of the heart, especially of the left ventricle, but unless high blood pressure or valvular disease is present in addition, cardiac enlargement is not a feature." We believe that our study shows definitely that coronary artery disease alone may lead to hypertrophy. The explanation given by Davis and Blumgart[145] is in line with what we believe to be probable. These authors postulated that with severe coronary sclerosis some hypertrophy results from impaired nutrition which causes the myocardial fibers to stretch and that the hypertrophy is greater in cases of congestive failure.

Dilatation of Hearts.—There was no significant dilatation of the chambers of the hearts in 360 (80 per cent) of the patients. Dilatation was slight or just noticeable in forty-two patients (9 per cent), moderate in twenty-four (5 per cent), and great in six (1 per cent). In some other patients dilatation of the right auricle and/or ventricle was noted, but unless this was great, the case was not included in the figures.

Myocardial Infarcts.—Gross infarcts were present in 114 patients. In sixteen patients there were two gross infarcts. Microscopic infarcts were present in twenty-three other patients, making a total of 137 patients with infarcts and a total of 153 infarcts. The locations of the infarcts, both gross and microscopic, are tabulated in Table XXXI. They were in the left ventricle and/or interventricular septum, left side, in all but seven patients, in whom they were in the posterior wall of the right ventricle. There were recent or fresh gross infarcts in sixty-eight patients, organizing gross infarcts in twenty-two, and old

gross infarcts in thirty-four; in six the age of the gross infarct was not noted. In thirty-one of the patients in whom the size of the gross infarcts was given, the diameter was from 0.5 to 1.9 cm., in sixteen it was from 2.0 to 3.9 cm., in six it was from 4.0 to 5.9 cm., and in six it was 6.0 cm. or more.

TABLE XXXI. LOCATION OF MYOCARDIAL INFARCTS (GROSS AND MICROSCOPIC) IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE*

LOCATION	NO.	%
Left ventricle, without localization	41	26.7
Left ventricle, anterior wall	34	22.2
Left ventricle, apex and interventricular septum	21	13.7
Interventricular septum, anterior third	14	9.2
Left ventricle, apex	13	8.5
Left ventricle, posterior wall	12	7.9
Interventricular septum, posterior upper part	6	3.9
Left ventricle, lateral wall	5	3.3
Right ventricle, posterior wall	7	4.6
Total	153	100.0

*There were 112 patients with gross and twenty-three patients with microscopic infarcts. In fourteen patients there were two infarcts and in two there were three infarcts. The infarcts were recent or fresh in ninety-two patients, organizing in twenty-three, and old in thirty-two; in six the age was not stated.

Myocardial Scarring.—Scars were present in the myocardium of 261 hearts, being diffuse in 155, focal in eighty nine, and diffuse and focal in seventeen. The exact extent of scarring was not definite, since usually only a few areas were examined microscopically.

State of the Coronary Arteries.—Due allowances must be made for the fact that many prosectors do not adequately examine all parts of the subepicardial coronary arteries. Sometimes they proceed no farther after finding some areas indicating disease. In forty-six patients the arteries showed neither sclerotic nor thrombotic occlusion but only thickening of the walls and narrowing of the lumina. It is quite possible that a diligent search might have uncovered more severe lesions, since these were unquestionably patients in whom death was the result of coronary artery disease, proved by clinical observations and by the absence of any other adequate cause of death; furthermore, in eight of these forty-six patients there were gross myocardial infarcts.

In 232 patients there was almost complete sclerotic occlusion in some part or parts of one or more coronary arteries, distributed as shown in Table XXXII. Here it is seen that the great preponderance of occlusions was in the proximal one-third of the left anterior descending artery. It must be pointed out, however, that various combinations existed. There was practically complete sclerotic occlusion of all three vessels in eighteen patients, of the left anterior descending and the left circumflex arteries in twenty-one, of the left anterior descending and right coronary arteries in nineteen, and of the left circumflex and right coronary arteries in two. In 229 patients there was thrombotic occlusion, recent, or-

ganizing, or old, in some part or parts of one or more coronary arteries, distributed as shown in Table XXXIII. Here, again, the occlusion was most often in the left anterior descending artery. There was, however, a difference in the distribution of the two forms of occlusion in the left circumflex artery, sclerotic occlusion existing in that artery in sixty patients, but thrombotic occlusion in only twenty-eight. In fifty-seven patients both sclerotic and thrombotic occlusions were present. Therefore, the totals were: sclerotic occlusion alone in 175

TABLE XXXII. ALMOST COMPLETE SCLEROTIC OCCLUSION OF CORONARY ARTERIES IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE*

LOCATION WITHIN ARTERY	CORONARY ARTERIES		
	LEFT ANTERIOR DESCENDING	RIGHT CORONARY	LEFT CIRCUMFLEX
Proximal alone	128	33	41
Medial alone	3	3	1
Distal alone	1	0	0
Proximal and medial	40	15	9
Proximal and distal	0	0	0
Medial and distal	0	0	0
Proximal, medial, and distal	8	4	3
Undifferentiated	12	4	6
Total	192	59	60

*Of these the following combinations existed: left anterior descending and left circumflex, 21 cases; left anterior descending and right coronary, 19 cases; left anterior descending, left circumflex, and right coronary, 18 cases; left circumflex and right coronary, 3 cases.

TABLE XXXIII. THROMBOTIC OCCLUSION OF CORONARY ARTERIES IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE*

LOCATION WITHIN ARTERY	CORONARY ARTERIES		
	LEFT ANTERIOR DESCENDING†	RIGHT CORONARY†	LEFT CIRCUMFLEX†
Proximal alone	129	34	20
Medial alone	7	4	1
Distal alone	2	0	0
Proximal and medial	23	7	5
Proximal and distal	0	0	0
Medial and distal	1	0	0
Proximal, medial, and distal	3	1	0
Undifferentiated	9	3	2
Total	174	49	28

*Of these the following multiple thrombi occurred, one in each location: left anterior descending and right coronary, nine; left anterior descending and left circumflex, four; right coronary and left circumflex, three; all three arteries, three.

†Thrombotic occlusion occurred in 229 cases. The thrombus was recent or fresh in 156 cases, organizing in nineteen, old in twenty, both old and fresh in twelve, and of unstated age in twenty-two.

patients; thrombotic occlusion alone* in 172; both sclerotic and thrombotic occlusion in fifty-seven. The thrombus was recent or fresh in 156 patients, organizing in nineteen, old in twenty, both old and fresh in twelve, and of unstated age in twenty-two.

From these figures, therefore, one is forced to conclude that coronary artery occlusion, both sclerotic and thrombotic, is greatly predominant in the left anterior descending artery, at least in this age group and probably in other age groups. This conclusion is in agreement with that of most authors[33,40,45,102,144]; the conclusion of Barnes and Ball[22] was the notable exception. Among our group of survivors, however, posterior infarctions were more than one-half as frequent as anterior infarction (28 per cent as compared with 44 per cent); there may be some justification, therefore, in the statement by some authors that acute occlusion of the right coronary artery carries a better prognosis than that of the left anterior descending artery. Our observations also confirm those of Saphir and associates,[133] who found the three main coronary arteries always involved by atherosclerosis. This was true, on the whole, in our series, although there were some exceptions. There were no cases of a single atheroma causing occlusion or being the site of the thrombus.

A summary of the pathogenesis of "coronary deaths" is given in Table XXXIV. This shows that 336 men died of coronary insufficiency without gross

TABLE XXXIV. SUMMARY OF PATHOGENESIS OF DEATHS FROM CORONARY DISEASE IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE

OCCLUSION	NO.	%
Patients without gross myocardial infarction	336	100.0
Without occlusion, sclerotic or thrombotic	38	11.3
With sclerotic occlusion alone	148	44.1
With thrombotic occlusion alone	117	34.8
With sclerotic and thrombotic occlusion	33	9.8
Patients with gross myocardial infarction*	114	100.0
Without occlusion, sclerotic or thrombotic	8	7.0
With sclerotic occlusion alone	27	23.7
With thrombotic occlusion alone	55	48.2
With sclerotic and thrombotic occlusion	24	21.1

*The age distribution of the infarcts was as follows: recent or fresh infarcts in fifty-six patients, one each; organizing infarcts in twelve patients, one each; old or healed infarcts in twenty-four patients, one each; one recent and one organizing infarct in each of six patients; one recent and one old infarct in each of six patients; one organizing and one old infarct in each of four patients; and one infarct of unstated age in each of six patients.

myocardial infarction, and that 114 died after the formation of gross infarcts. Death resulted from coronary insufficiency without gross infarction or coronary occlusion in thirty-eight patients. Gross infarcts were present in eight men without coronary artery occlusion. Gross infarcts were much more frequent with thrombotic occlusion and thrombotic and sclerotic occlusion combined, than with sclerotic occlusion alone. The number of deaths in the patients without gross infarction was greater with sclerotic occlusion alone than with the total of

*The thrombus forming, of course, in sclerotic vessels.

thrombotic occlusions and thrombotic and sclerotic occlusions combined. The possibility of spasms of the collateral and unaffected smaller coronary arteries in the production of coronary insufficiency and angina pectoris, as postulated by Leary[146] and Gilbert,[147] cannot be confirmed or denied in morphologic studies such as this. It will be very difficult to settle this point; we are inclined to doubt that the factor of spasm is important in most cases. On the other hand, the results of the study of this series are in line with the work and conclusions of Blumgart, Schlesinger, and Davis[118] and Blumgart, Schlesinger, and Zoll.[123] Although the injection method of examination was not used in this series, the fact that in about one-half of the patients who died there were no known symptoms prior to the fatal attack, in spite of advanced artery disease, leads one to think that intercoronary communication of importance probably had developed.

The large number of coronary deaths without infarction in our series stimulated us to look up the literature on this subject. Among twenty-three cases studied by Wolff and White,[1] six of the patients died as the result of coronary artery occlusion without infarction. Appelbaum and Nicholson[54] had thirteen such patients among 150 cases of occlusion. Wright-Smith[58] reported a series of 495 cases of coronary artery occlusion with only eighty-seven infarctions; 224 of the cases were instances of sudden death. Benson[64] presented a case report of a 34-year-old pilot who suffered an attack of acute chest pain while flying and died twenty minutes after landing the plane; autopsy revealed atherosclerosis of both right and left coronary arteries, but there was no acute occlusion and no infarction. Jokl and Melzer[70] reported twenty cases of sudden death due to cardiac causes; four of the patients showed marked coronary artery sclerosis without infarction. Levy and Bruenn[93] studied twenty-four cases of coronary death selected on the basis of coronary sclerosis without thrombosis.

Coronary insufficiency without thrombosis of a coronary artery is not uncommon. In the series of 150 cases of Appelbaum and Nicholson,[54] there were thirty-seven patients with marked sclerotic narrowing but without coronary thrombosis in which an infarct was encountered. Nathanson[34] observed only twenty-four of 113 patients with fatal coronary artery disease in whom a coronary thrombus was found. Lisa and Ring[45] noted coronary thrombosis in thirteen of thirty-two patients with fresh myocardial infarction; among sixty-eight patients with healed infarcts, coronary thrombosis was recognized in eleven. In the study of 495 cases by Wright-Smith[58] there were 339 coroner's cases, in 314 of which (92.9 per cent) there was atheromatous occlusion and in only twenty-four (7 per cent), coronary artery thrombosis. Of his 156 hospitalized patients, 135 (86.6 per cent) had atherosclerotic occlusion and twenty-one (13.4 per cent), thrombotic occlusion. In Bean's[144] series of 300 cases, 20 per cent of the patients (with fifty-eight infarcts) had arterial narrowing without thrombosis. Gross and Sternberg[149] reported fifteen cases of myocardial infarction without demonstrable occlusion of the coronary arteries. In a study of 153 cases of myocardial infarction, infarction in the absence of thrombotic occlusion occurred in thirty-seven patients; there were six patients in whom the only pathologic feature to which infarction could be ascribed was severe narrowing of the coronary arteries. Meesen[84] reported two series of cases of sudden death due to heart disease. In

one series there were 475 patients, of whom 188 had coronary sclerosis with thrombosis and 287 had sclerosis without thrombosis. The second series was made up of 115 cases, in which there were forty-nine patients with coronary sclerosis with thrombosis and sixty-six with sclerosis without thrombosis.

Nathanson[34] sums up the situation well by stating that "A prolonged attack, consisting of initial shock which the patient survives, is more frequent with a thrombus. Such a picture does occur, however, in coronary sclerosis without thrombosis." He states further that it is more reasonable to regard thrombosis not as an entity but merely as one of the end results of coronary disease occurring in approximately 20 per cent of the cases. Our experience with this large group of younger men leads to a somewhat different, although, in general, similar conclusion. We find that sudden death without infarction is more common in those with sclerotic occlusion alone, but that death from coronary artery disease is associated with coronary thrombosis in about 50 per cent of the cases. Our series demonstrates, too, that myocardial infarction may occasionally result from ischemia due to coronary artery sclerosis without either sclerotic or thrombotic occlusion.

The Microscopic Lesions of the Coronary Arteries and Myocardium.—There was no difference in the histologic appearance of the coronary lesions in the patients of this series from those described many times as coronary arteriosclerosis. There were no clear-cut cases of thromboangiitis obliterans, periarteritis nodosa, or rheumatic arteritis.[150]

The atheromatous plaque was the prominent lesion which reduced the vascular lumen (Figs. 7 and 8). The plaques were more frequently eccentric than annular in disposition (Fig. 9). They usually had thin zones of mixed fibrous and collagenous connective tissue which rested on the remnants of the internal elastic lamina. Vascularization of the plaques, present to some extent in about one-half of the patients, was usually most prominent at their margins and bases (Fig. 10). The plaques frequently contained a central nidus of cholesterol crystals, lipophages of various forms, amorphous material, and occasionally fine granules of calcium (Figs. 11, 12, 13, 14, 15, and 16). Less frequently larger masses of calcium were encountered. These atheromatous deposits were covered by a zone of hyalinized connective tissue which outlined the remaining lumen. Occasionally the surface zone was composed of more cellular, vascular connective tissue in which small deposits of fibrinoid material were found. An endothelial lining was rarely demonstrable. The lumen in all patients was reduced, in many instances to the extent that there was little or no opening left.

After much study it was decided that sclerosis of the coronary arteries could be grouped into three grades on the basis of age of the disease, although there is no way of determining just how old the lesion is, since the degenerative process may develop faster in some patients than in others and since the rate of development may vary in different parts of the arterial tree. There is, of course, some overlapping of the various features. The classification is as follows:

GRADE 1. EARLY ATHEROSCLEROSIS (FIG. 17)

1. Simple plaque formation, the plaque being composed chiefly of moderately loosely arranged connective tissue frequently containing young fibroblasts
2. Absence of calcium
3. Presence only occasionally of a small nidus of amorphous material in the plaque
4. Slight, if any, vascularization of plaque or media
5. Few, if any, cholesterol crystals in the plaque
6. Slight to moderate damage to the internal elastic lamina, which usually may be identified
7. Slight thinning with minimal interstitial fibrosis of the media below the plaque

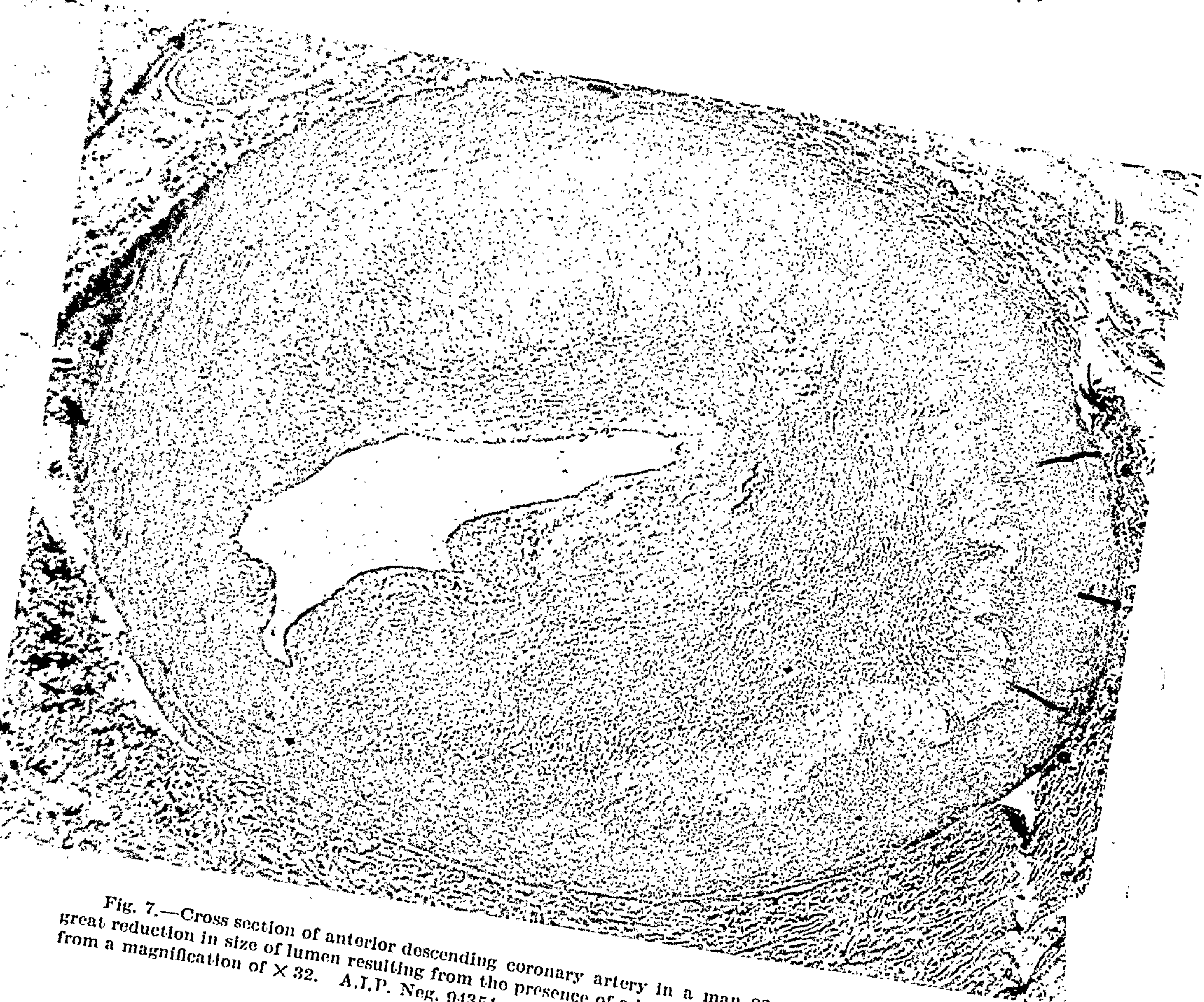

Fig. 7.—Cross section of anterior descending coronary artery in a man 22 years of age, showing great reduction in size of lumen resulting from the presence of a large atheromatous plaque. Reduced from a magnification of × 32. A.I.P. Neg. 94354.

GRADE 2. MODERATELY ADVANCED ATHEROSCLEROSIS (FIG. 9)

1. Hyalinized base of the plaque
2. Presence of a large mass of amorphous cholesterol or lipid in the plaque
3. Surface of plaque composed of compact fibrous tissue in which a few fibroblasts persist
4. Minimal calcium deposition in center of plaque usually in the form of fine calcium granules or calcified nuclei of fibroblasts
5. Presence of a few cholesterol clefts
6. Slight marginal vascularization
7. Fragmentation or frequent absence of internal elastic lamina
8. Moderately thin, occasionally vascularized media, with loss of muscle fibers and increased fibrosis below plaque

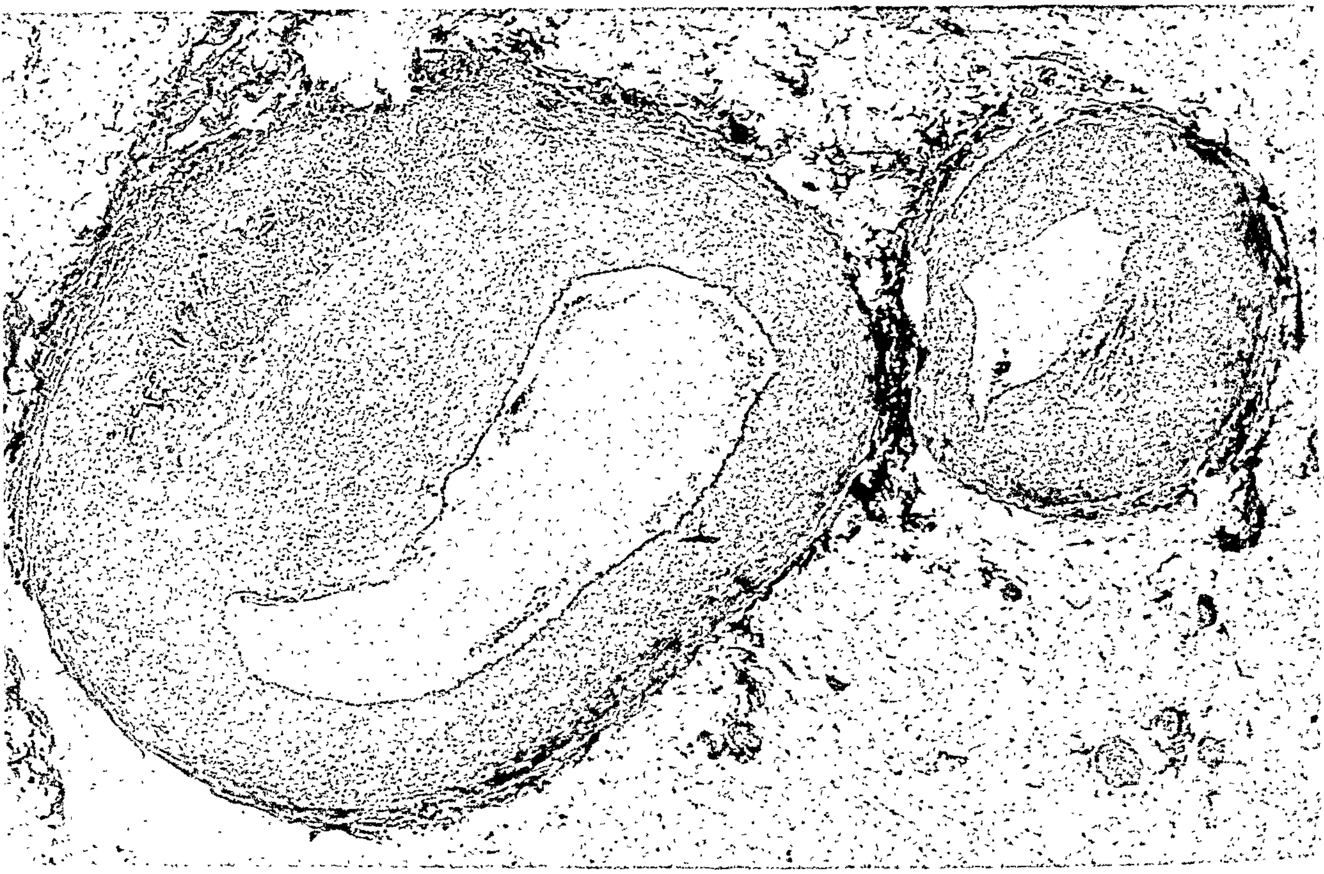

Fig. 8.—Sclerosis of coronary artery and a secondary branch (simple narrowing), showing that coronary artery disease is generalized, a not uncommon finding. Man 34 years of age. Reduced from a magnification of × 30. A.I.P. Neg. 94231.

GRADE 3. ADVANCED ATHEROSCLEROSIS (FIG. 11)

1. Complete or almost complete hyalinization of the plaque, both base and surface zones, with fibroblasts remaining only at margins
2. Masses of calcium in plaques
3. Frequent presence of cholesterol clefts
4. Common presence of broad vascular channels at margin and base of plaque
5. Absence of or severe damage to internal elastic lamina
6. Hyalinization or atrophy of media, with loss of muscle and increase in fibrous tissue

GENERAL OBSERVATIONS

1. Size of plaque bears little relation to age of lesion
2. Cellular infiltration with lymphocytes and plasma cells either in plaque or adventitia bears little relation to age of lesion, although it is slightly more common in the younger lesions.

Fig. 9.—Large eccentric atheromatous plaque in coronary artery of a man 23 years of age (Grade II atherosclerosis). Weigert's elastic tissue stain. Reduced from a magnification of × 30. A.I.P. Neg. 94236.

Table XXXV shows the distribution of the three grades of atherosclerosis on the basis of this classification among 308 patients, compared with 151 patients of a 40- to 49-year age group. This table shows well how the age of the atherosclerosis advances with the ages of the patients according to the method of grading adopted. This method of gradation is somewhat at variance with that of Leary,[48,151,152,153] but it appeals to us as being more logical, since the degenerative changes of the media definitely progress as our grades of atheromatosis advance. Thus, actually from the changes of the media one is able to establish the relative age of the atheromatous plaque.

TABLE XXXV. DISTRIBUTION OF GRADES OF ATHEROSCLEROSIS BY AGE GROUP OF PATIENTS

GRADE OF ATHEROSCLEROSIS	AGE GROUPS									
	18 TO 24 YEARS		25 TO 29 YEARS		30 TO 34 YEARS		35 TO 39 YEARS		40 TO 49 YEARS	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
I	17	68.0	39	66.1	26	27.4	9	7.0	1	0.7
II	5	20.0	9	15.3	46	48.4	33	25.6	36	23.8
III	3	12.0	11	18.6	23	24.2	87	67.4	114	75.5
No. of Cases	25		59		95		129		151	

Note: Grade II includes one patient in the 18- to 24-year age group, two in the 25- to 29-year age group with both Grades I and II, and Grade III includes sixteen patients in the 40- to 49-year age group with both Grades II and III, and one patient with Grades I, II, and III. The total number of patients compared is, therefore, 459.

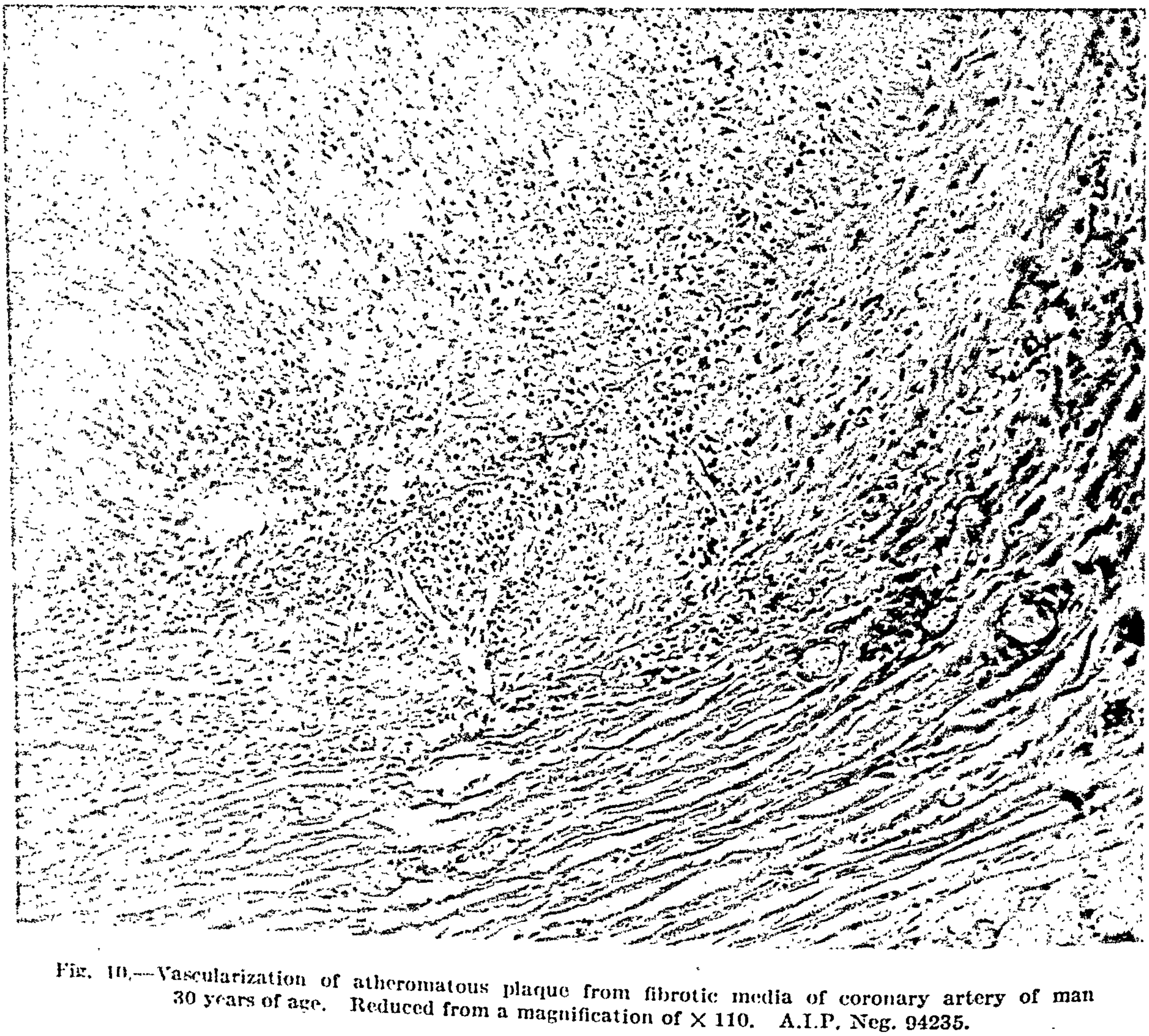

Fig. 10.—Vascularization of atheromatous plaque from fibrotic media of coronary artery of man 30 years of age. Reduced from a magnification of × 110. A.I.P. Neg. 94235.

It seems to us that one must preserve an open mind as to the importance of disturbance of cholesterol metabolism in the pathogenesis of atheroma. There is still the possibility that the deposition of lipids in the plaque is secondary rather than primary. As our material seems to show, the first stage in the life history of the atheromatous plaque is mainly that of fibroblastic proliferation of the intima; the second stage, the deposition of lipids and their ingestion and liquefaction by macrophages; and the third stage, hyalinization, with remnants of lipids in the form of cholesterol crystals remaining. Leary's excellent work, however, even though the conclusions may not be final, has done much to stimulate thought and study of the problem of atherosclerosis.

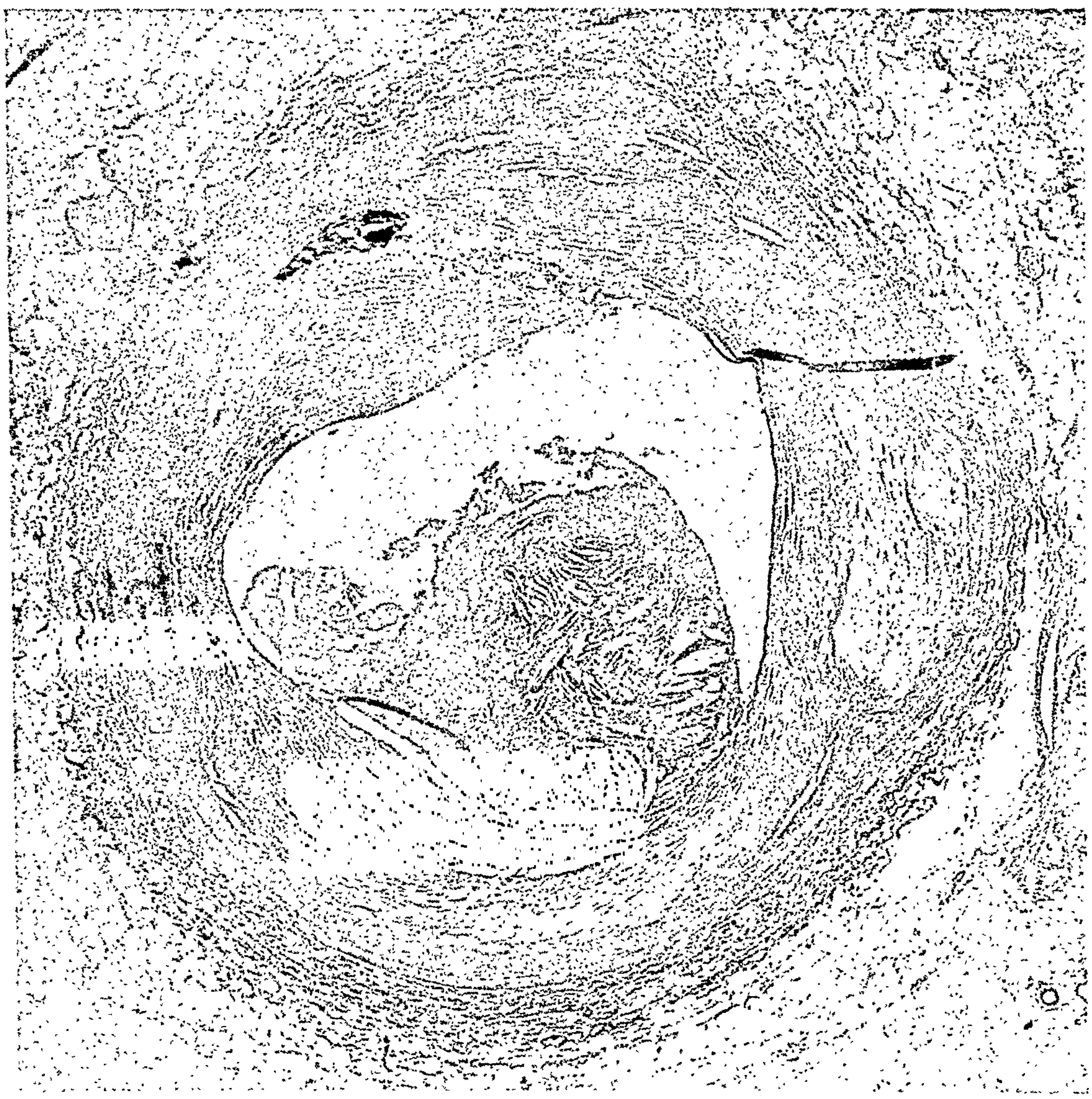

Fig. 11.—Atheromatous plaque with central nidus of cholesterol clefts in a man 36 years of age (Grade III atherosclerosis). Reduced from a magnification of × 30. A.I.P. Neg. 94233.

In approximately 35 per cent of the patients of this series recent thrombotic occlusion of the persisting lumen occurred (Figs. 18 and 19). In approximately another 9 per cent the thrombus was undergoing organization or was so old that it was a mass of scar tissue (Figs. 20, 21, and 22). Some of these thrombi were

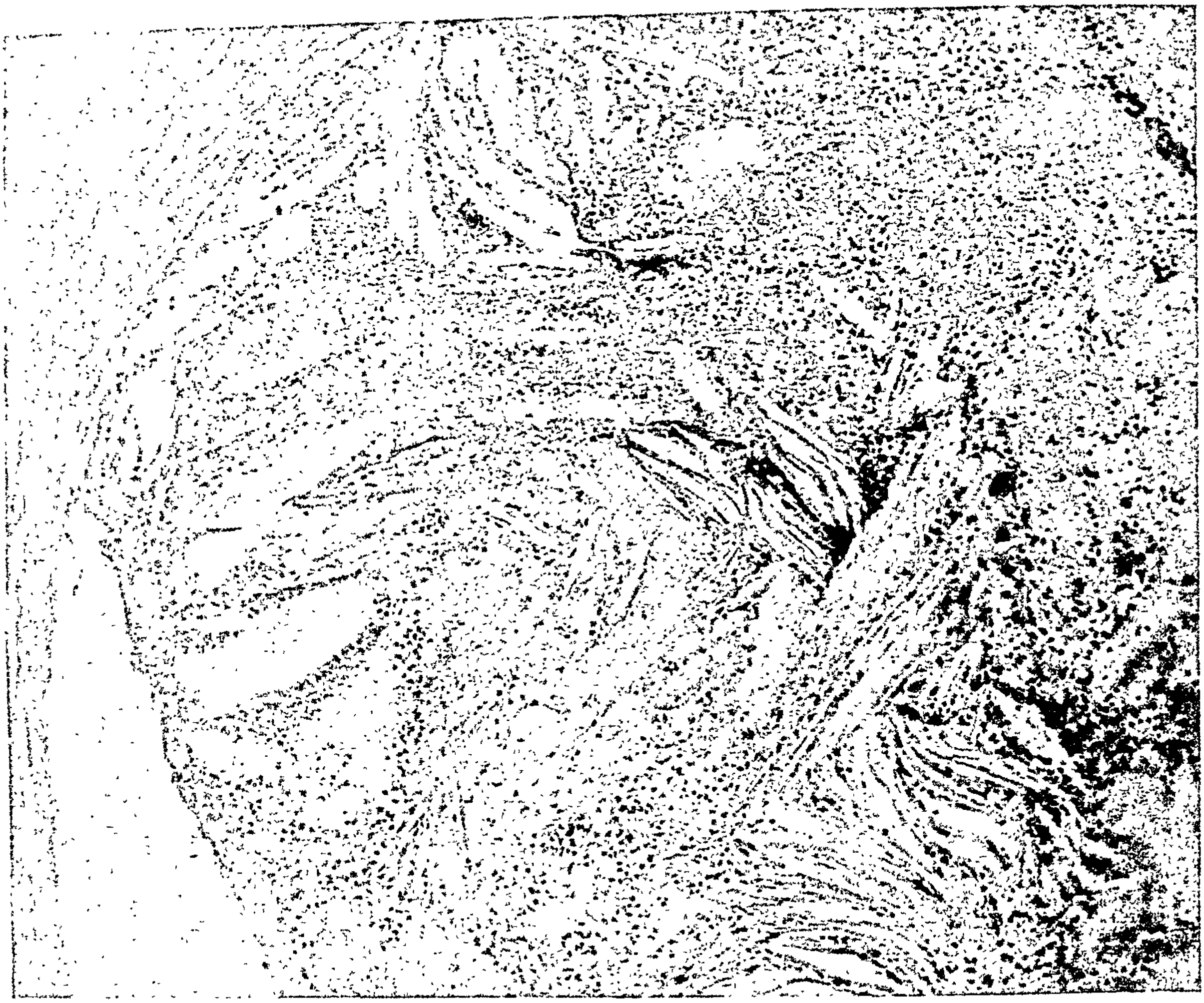

Fig. 12.—Cholesterol clefts in plaque shown in Fig. 5, reduced from a magnification of ×110. A.I.P. Neg. 94234.

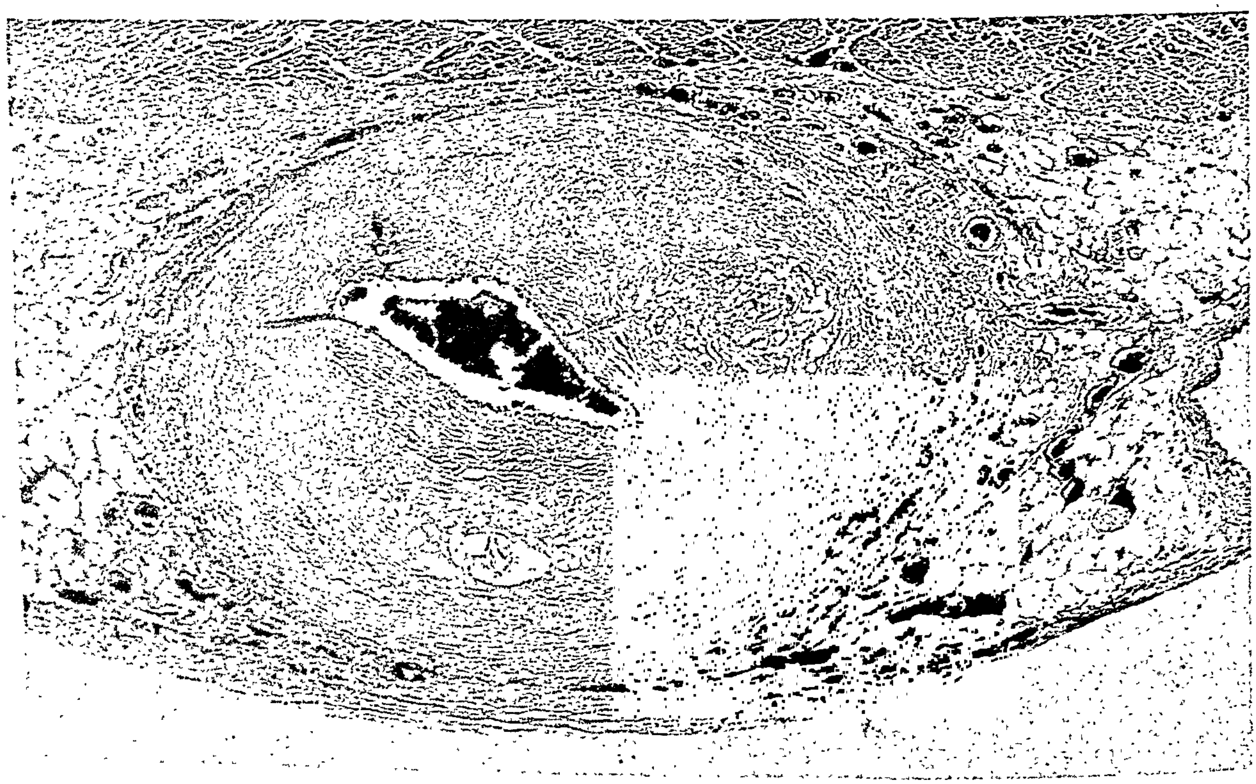

Fig. 13.—Coronary artery of a man 30 years of age, showing so-called atheromatous abscess. Reduced

recanalized, but the channels were so tortuous that only an insignificant column of blood could have passed through them (Figs. 23 and 24).

Below the site of plaque formation the internal elastic lamina was usually fragmented, reduplicated, ironed out, or completely absent, and the media was thin and atrophic. Infiltration of the media by round cells, chiefly lymphocytes, was rare (Fig. 25). There was slight to moderate adventitial fibrosis, most pronounced in that segment directly related to the position of the plaque. Occasionally there was moderate to dense infiltration of the adventitia by mononuclear cells, chiefly lymphocytes, but occasionally plasma cells.

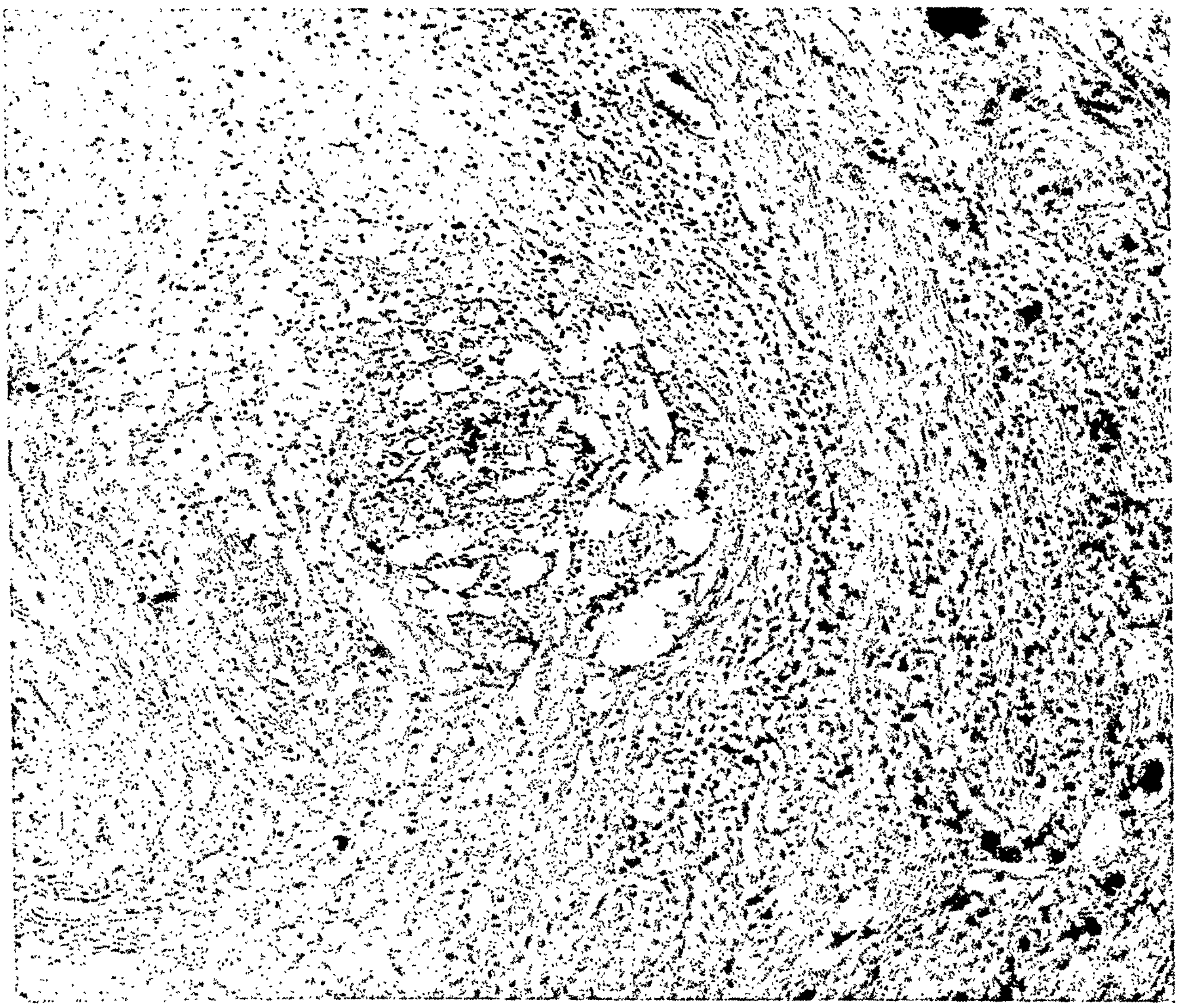

Fig. 14.—High-power view of so-called atheromatous abscess of artery shown in Fig. 7. Note lipophages and mononuclear infiltration. Reduced from a magnification of × 30. A.I.P. Neg. 94241.

Recent hemorrhage (Fig. 26) in the plaque was found in twenty-six patients (5.8 per cent) and old hemorrhage in twenty-nine (6.4 per cent). Both fresh and old hemorrhages were present in five of these. The incidence of hemorrhage in the plaque was much less than that given in the literature by Winternitz and associates,[154] by Wartman,[155] by Paterson,[156] by Horn and Finkelstein,[157] and by Field.[158] From our experience, therefore, we have not been impressed with the

importance of intramural hemorrhage, but it must be admitted that had serial sections of the vessels been studied, more cases of such hemorrhage might have been found. Also, we found that in the younger age groups there were fewer instances of the more advanced atheromatous lesions, and that there was a high incidence of deaths from coronary insufficiency without thrombosis. Table XXXVI shows the salient data of the coronary arteries as to the presence and age of thrombi, hemorrhage in, and rupture in the plaque according to age groups. This table shows insignificant differences in these factors in the different age groups up to 50 years.

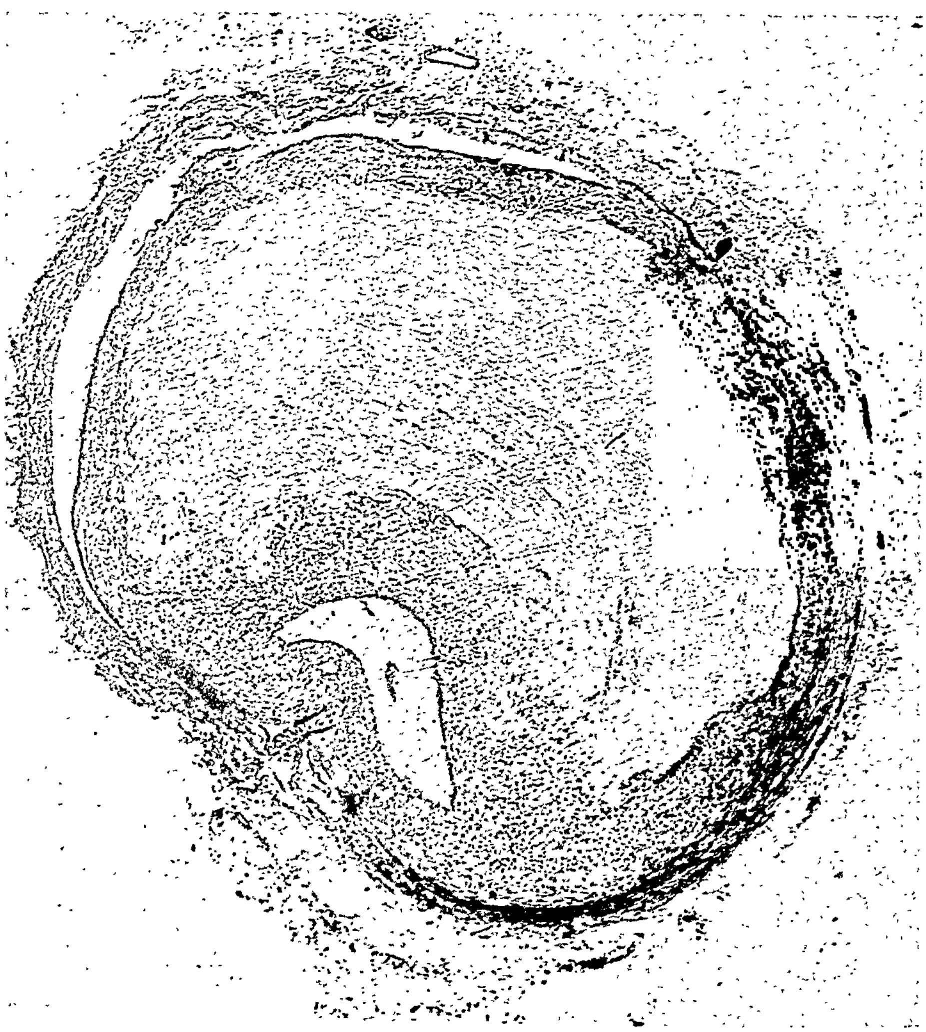

Fig. 15.—Atheromatous plaque with large nidus of amorphous material and small eccentric lumen (practically complete sclerotic occlusion). Man 20 years of age. Reduced from a magnification of ×30. A.I.P. Neg. 94115.

The myocardial lesions were variable in degree and age. Recent infarctions grossly resembled those commonly described. The areas of recent gross infarction were pale gray or yellowish gray, soft, and granular, and on section stood slightly above the adjacent pinkish gray or russet brown myocardium.

Table XXXVI. Coronary Thrombi, Hemorrhage in Plaque, and Rupture in Plaque by Age Groups in Hearts Examined Microscopically

Lesion	Age Group									
	18 to 24 Years		25 to 29 Years		30 to 34 Years		35 to 39 Years		40 to 49* Years	
	No.	%	No.	%	No.	%	No.	%	No.	%
Recent thrombus	9	36.0	12	20.3	23	24.2	28	21.7	45	29.0
Organizing or old thrombus	4	16.0	6	10.2	12	12.6	16	12.4	15	9.7
Total number with data	25		59		95		129		155	
Hemorrhage in plaque	4	16.0	11	18.6	16	16.8	20	15.5	20	13.0
Total number with data	25		59		95		129		154	
Rupture in plaque	0	0.0	0	0.0	4	4.2	10	7.8	6	5.8
Total number with data	25		59		95		129		103	

*The 40- to 49-year age group includes eight patients with both recent and old and one patient with both recent and organizing thrombi.

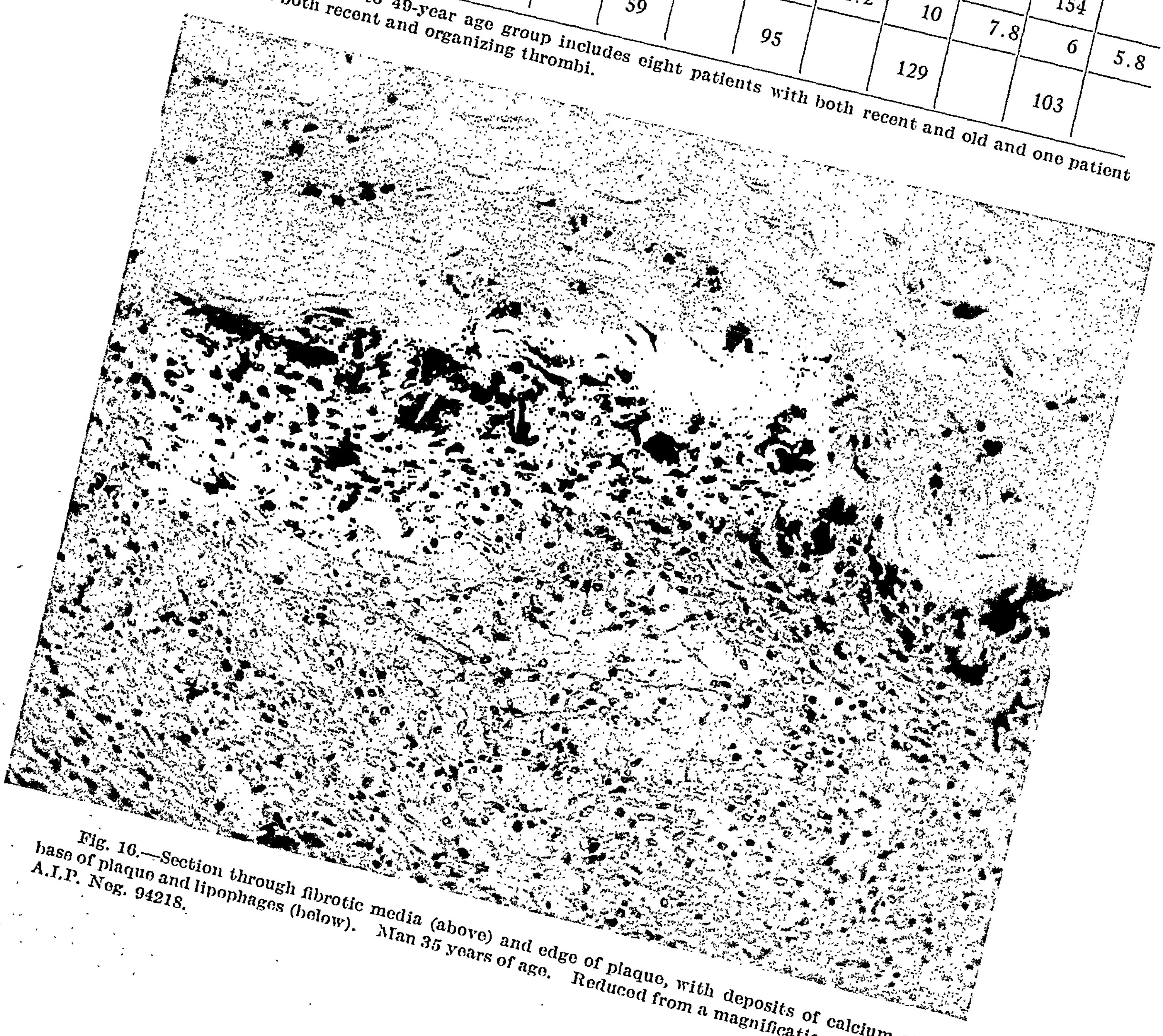

Fig. 16.—Section through fibrotic media (above) and edge of plaque, with deposits of calcium at base of plaque and lipophages (below). Man 35 years of age. Reduced from a magnification of × 235. A.I.P. Neg. 94218.

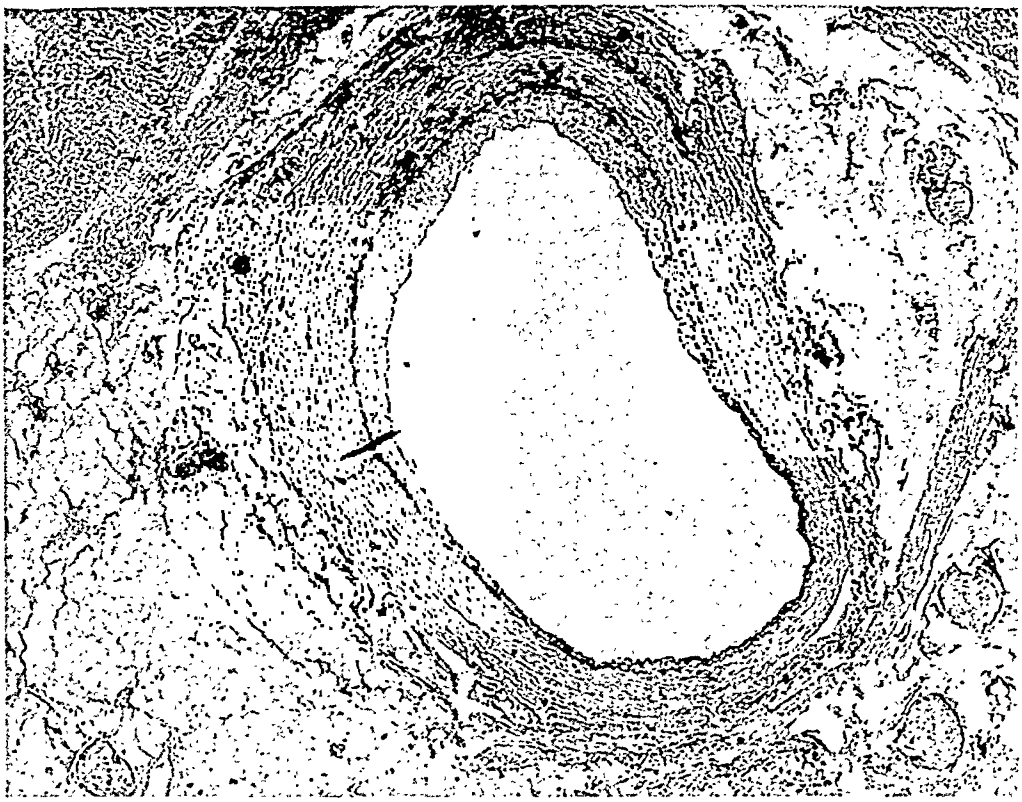

Fig. 17.—Grade I atherosclerosis. Man 23 years of age. Reduced from a magnification of × 25. A.I.P. Neg. 100253.

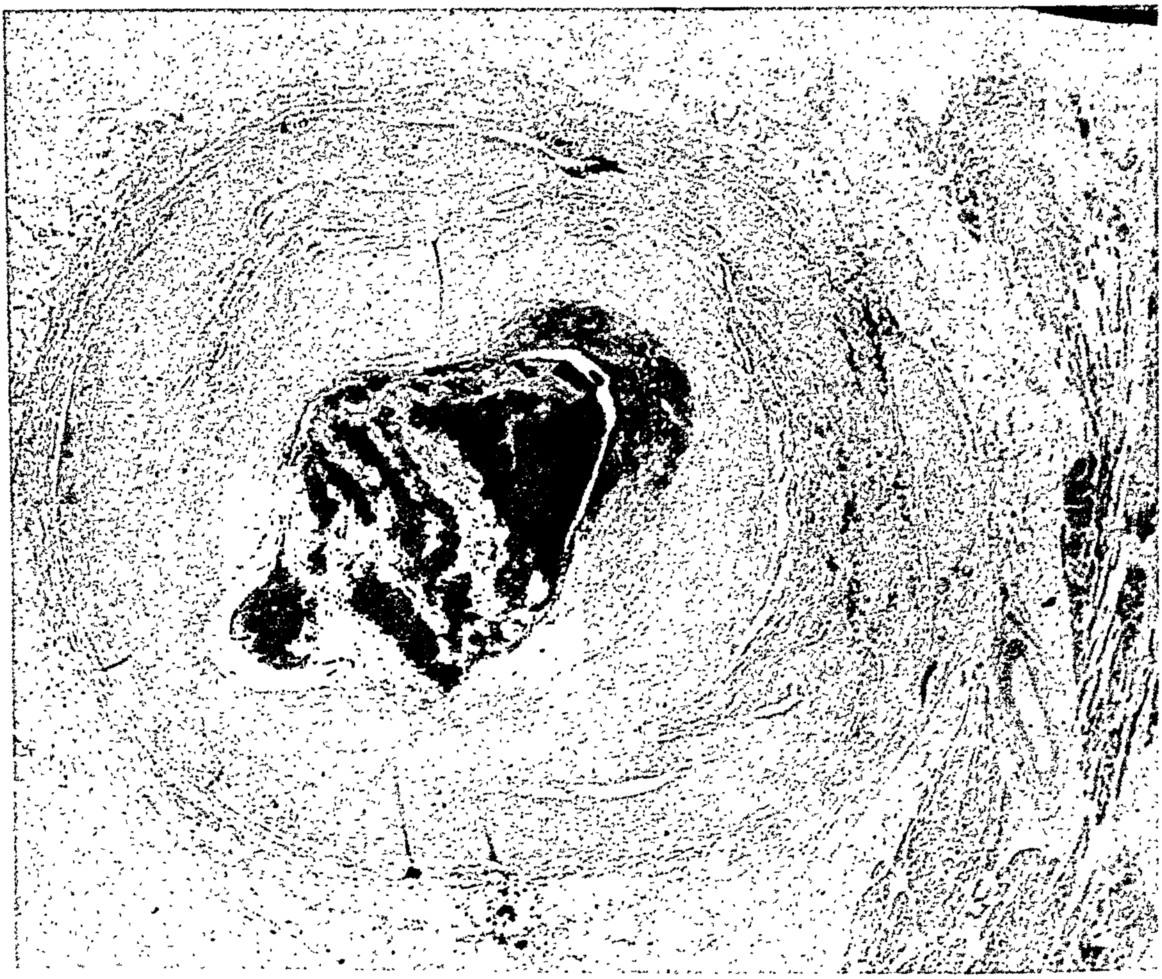

Fig. 18.—Fresh thrombus filling reduced lumen of sclerotic coronary artery of man 24 years of age. Reduced from a magnification of × 16. A.I.P. Neg. 94244.

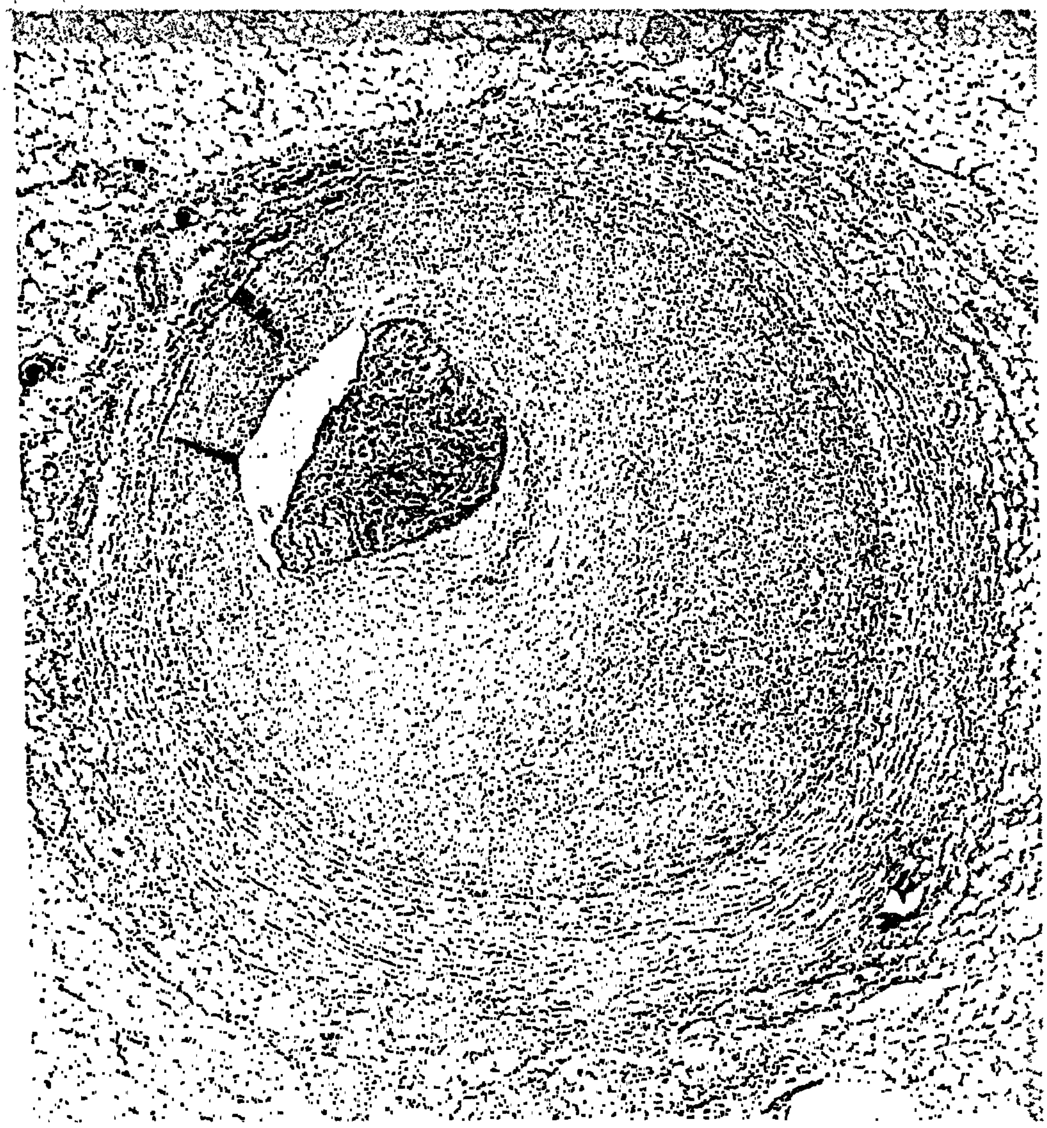

Fig. 19.—Fresh thrombus filling small lumen of sclerotic coronary artery of man 35 years of age.]
duced from a magnification of × 26. A.I.P. Neg. 94229.

Fig. 20.—Organizing thrombus filling small lumen of sclerotic coronary artery of man 30 years of ag
Note adventitial fibrosis. Reduced from a magnification of × 25. A.I.P. Neg. 94237.

Organizing gross infarcts were light gray, semitranslucent, and moderately firm, and frequently exhibited patchy zones which were slightly sunken or depressed. Gray trabeculations were interspersed by sunken zones which appeared slightly gelatinous in character.

Old gross infarcts were of firm, opaque, white fibrous tissue, usually slightly depressed, and frequently sending fibrous trabeculations into the adjacent myocardium.

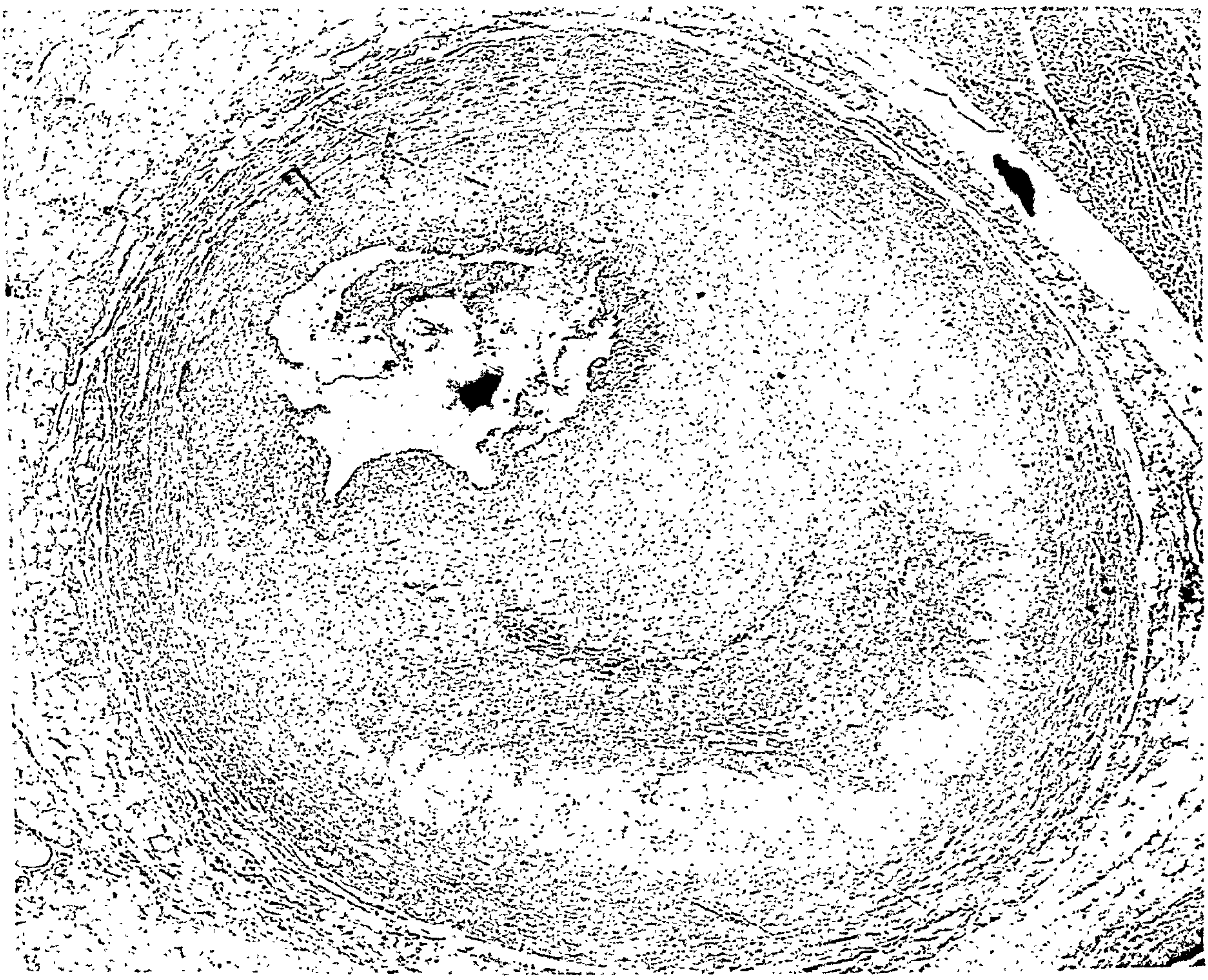

Fig. 21.—Organizing thrombus in lumen of sclerotic coronary artery of man 25 years of age. Note semilunar zone of amorphous material near base of plaque. Reduced from a magnification of × 25. A.I.P. Neg. 94222.

Microscopically, in recent infarctions there was necrosis of the myocardial fibers, pyknosis, karyorrhexis or karyolysis of nuclei, and dense infiltration of the area by polymorphonuclear leucocytes.

In organizing infarctions there was deposition of cellular fibrous connective tissue which was well vascularized by recently formed capillaries and sparsely infiltrated by mononuclear cells and phagocytes. Some of the adjacent viable fibers were hypertrophied. The arteries and arterioles frequently showed medial

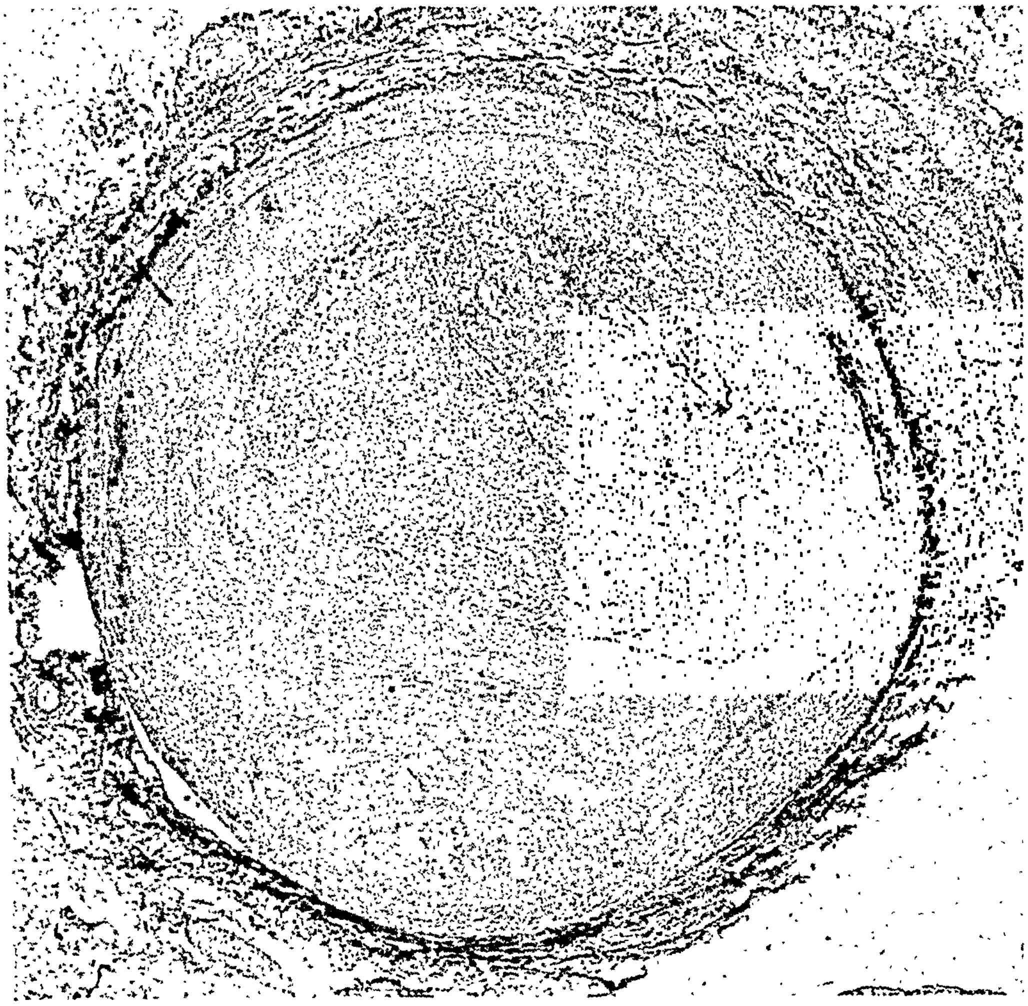

Fig. 22.—Organized thrombus filling lumen of sclerotic coronary artery of man 39 years of age. Reduced from a magnification of × 20. A.I.P. Neg. 94243.

hypertrophy in the zones of infarction, but they were rarely occluded by thrombi and never sclerotic.

In old infarcts there was replacement of broad zones of myocardial fibers by dense hyalinized fibrous tissue. Occasionally, sparse mononuclear leucocytic infiltration occurred in the region of these scars.

Table XXXVII shows the distribution of infarcts, recent, organizing, and old, diffuse fibrosis, focal scars, and mural thrombi in a special histologic study of the various age groups, including a 40- to 49-year age group.

Mural Thrombi.—Mural thrombi were present in forty-three patients: thirty-seven in the left ventricle, five in the right, and two in both. They ranged in size from less than 0.5 cm. to more than 6 cm. in diameter. They were responsible for hemiplegia in three patients at the clinical onset of the terminal illness and for five more clinically recognizable embolizations during the course of the illness.

The percentage of mural thrombi in this series is somewhat lower than that usually found in cases involving all ages, the average figures being 45 per cent.[144] Based on the 114 cases of gross myocardial infarction in this series, the percentage

TABLE XXXVII. MYOCARDIAL INFARCTS, DIFFUSE FIBROSIS, FOCAL SCARS, AND MURAL THROMBI AMONG DIFFERENT AGE GROUPS, IN HEARTS EXAMINED MICROSCOPICALLY

LESION	AGE GROUP									
	18 TO 24 YEARS		25 TO 29 YEARS		30 TO 34 YEARS		35 TO 39 YEARS		40 TO 49 YEARS	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Infarcts	8	32	14	24	26	27	40	31	76	44
Recent	4	16	4	7	6	6	13	10	37	21
Organizing	3	12	7	12	14	15	16	12	14	8
Old	1	4	3	5	6	6	11	9	11	6
Diffuse fibrosis	2	8	6	10	16	17	14	11	56	32
Focal scars	3	12	12	20	23	24	29	23	83	48
Mural thrombus	2	8	2	3	4	4	5	4	24	30
Total number with data	25		59		95		129		174	

The 30- to 39-year age group includes three patients with both recent and old, seven with recent and organizing, and four with organizing and old infarcts.

In the 40- to 49-year age group, the corresponding figures were: eight recent and organizing, one organizing and old, and two recent, organizing, and old infarcts.

The total number of infarcts found was seventy-six, but the age of infarct was not determined in fourteen of the patients.

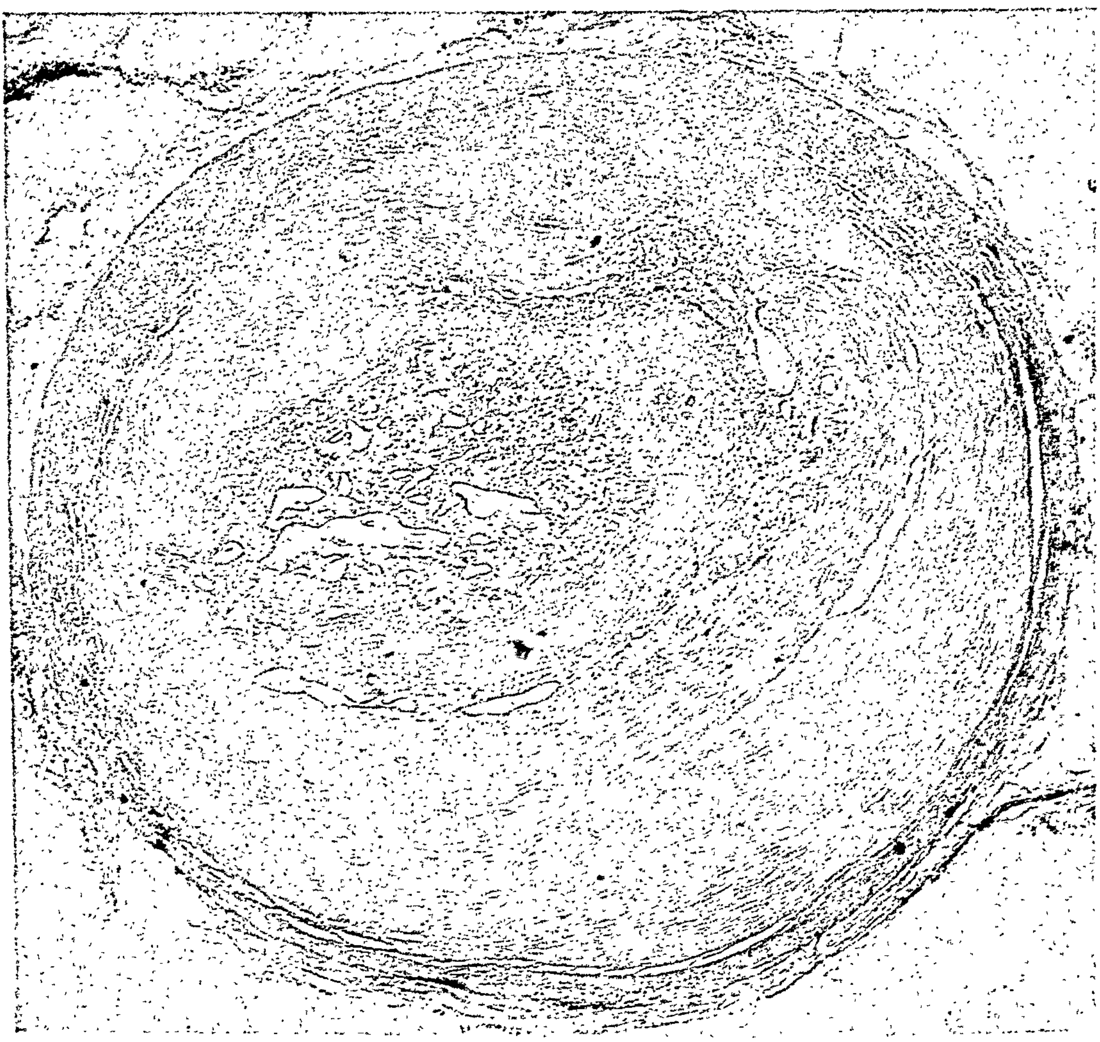

Fig. 23.—Recanalized thrombus filling lumen of sclerotic coronary artery of man 39 years of age. Reduced from a magnification of × 25. A.I.P. Neg. 94228.

is 38. The percentage of recognized embolization, 19, is quite low. There were in the present series, however, other infarcts discovered at necropsy, especially in the lungs, kidneys, and spleen, which were either not recognized during life or which in themselves were not considered significant in the causation of death; these are not included in the 19 per cent. Bean [144] reported 34 per cent of systemic emboli in the patients in whom the thrombus was in the left ventricle.

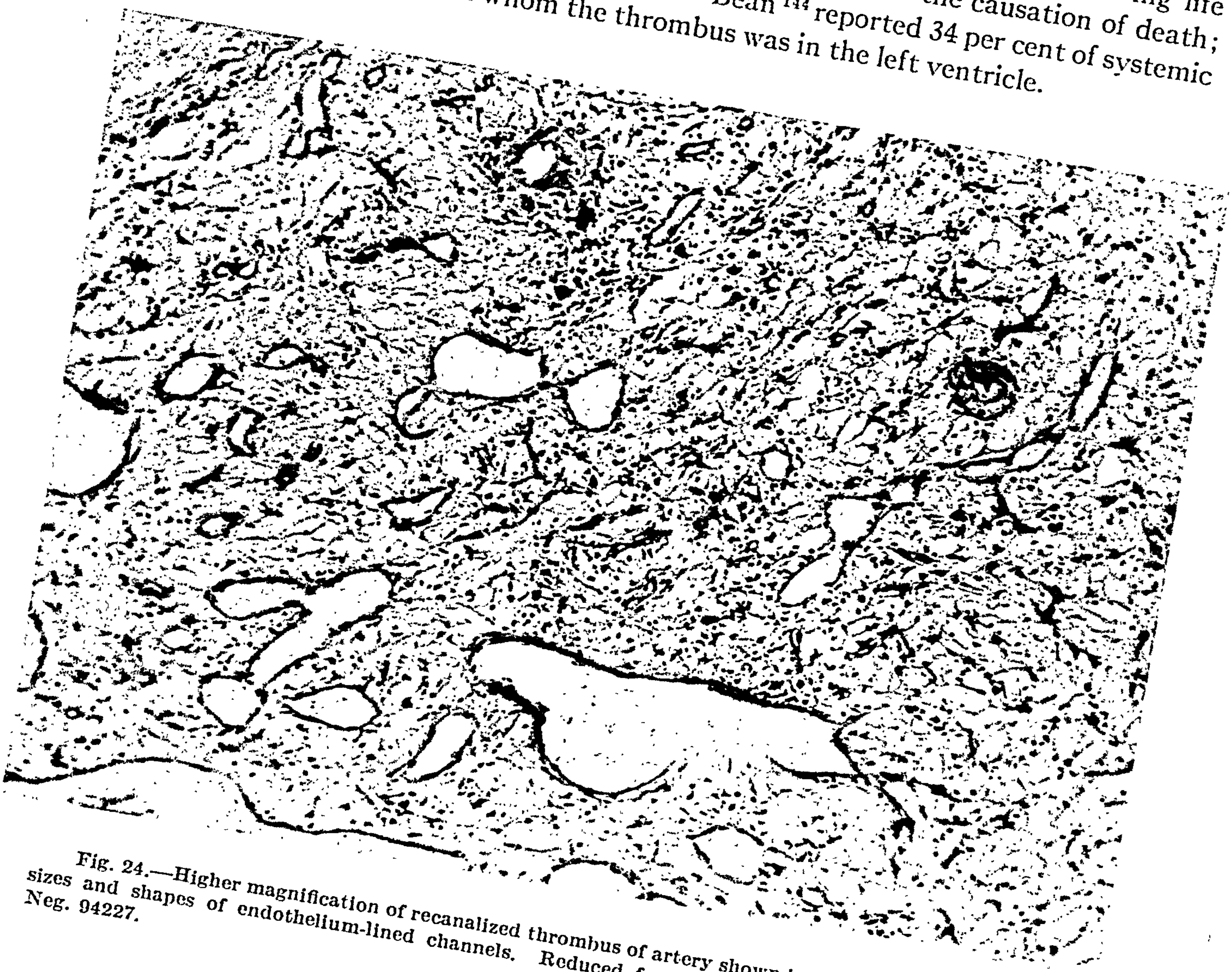

Fig. 24.—Higher magnification of recanalized thrombus of artery shown in Fig. 15, showing various sizes and shapes of endothelium-lined channels. Reduced from a magnification of × 110. A.I.P. Neg. 94227.

Valvular Abnormalities.—In ninety-three patients there were valvular lesions, eighty-two of which were plaques, nodulations, or fenestrations of no importance. The mitral valve was the site of rheumatic scarring with slight to moderate stenosis in seven patients, the aortic valve in one patient, and the mitral and aortic valves together in two patients. In one patient there was syphilitic aortitis with aortic regurgitation, as previously mentioned.

Pericardial Lesions.—The hearts of twenty-three patients presented petechiae of the visceral pericardium, ranging from few to many, more often the former. In fourteen patients with petechiae there were fresh myocardial infarcts. In one of the patients there were both fibrous and old pericardial

adhesions associated with a fresh and an old infarct. In five of the patients there was also focal fibrinous pericarditis, all with infarcts. In one patient there were old pericardial adhesions with an old infarct.

In twelve patients there was focal fibrinous pericarditis, and in all twelve of these there were fresh myocardial infarcts. In four of the twelve patients there were also pericardial petechiae. In one of the twelve patients the peri-

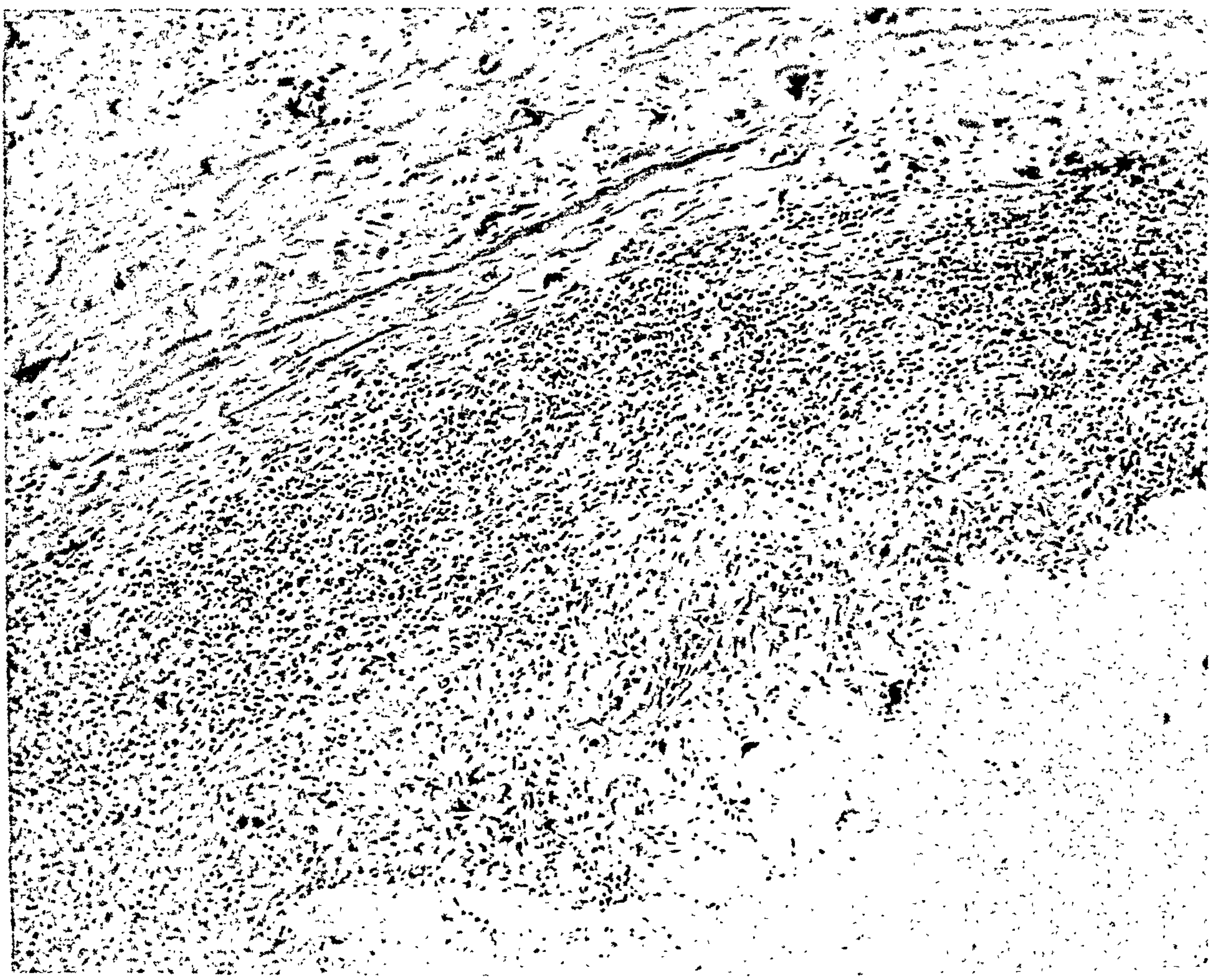

Fig. 25.—Infiltration of media of sclerotic coronary artery by mononuclear cells in a man 28 years of age. Reduced from a magnification of × 110. A.I.P. Neg. 94224.

cardium was also edematous, and in another there was 70 c.c. of a flaky, whitish exudate. In two of the twelve patients there were also patches of old fibrous adhesions. In a thirteenth patient the entire heart was encased in a fibrinous exudate ranging from 1 to 4 mm. in thickness, and there was a massive, fresh infarct of the left ventricle and interventricular septum. The incidence of acute pericarditis for the eighty-four patients with recent or organizing infarcts is, therefore, 15.5 per cent, whereas in the literature the incidence has been reported to be 28 per cent.[144]

In eight men there were patches of old fibrous adhesions; in four of these there were fresh infarcts and in two, old infarcts. Two of these patients also presented areas of fibrinous pericarditis. In a ninth patient the whole pericardial sac was obliterated by the old adhesions, and in a tenth the entire right ventricle was involved, with a calcified mass in the pericardium measuring 4 by 3 centimeters.

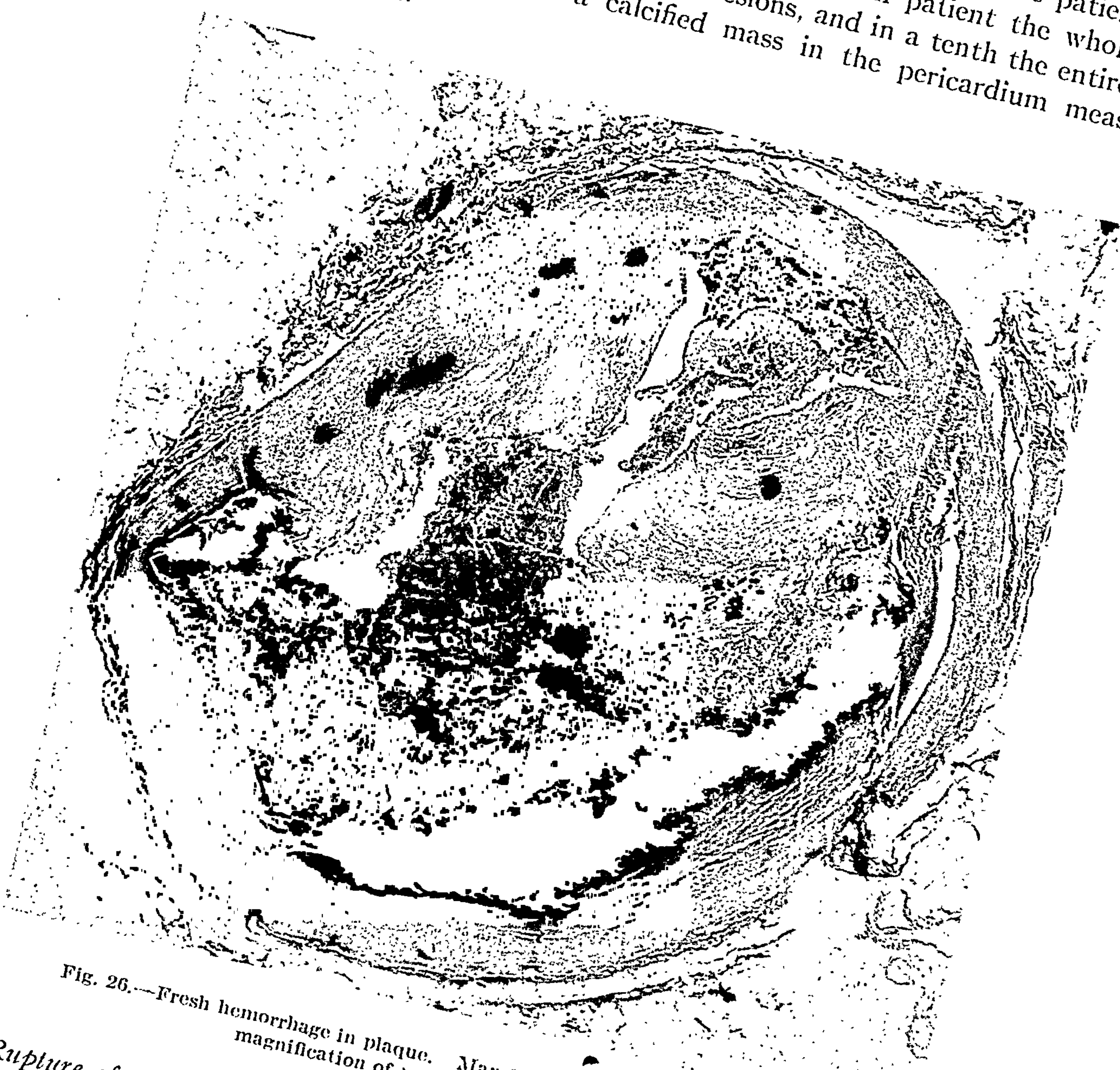

Fig. 26.—Fresh hemorrhage in plaque. Man 26 years of age. Reduced from a magnification of × 25. A.I.P. Neg. 94116.

Rupture of the Heart.—There were four cases of rupture of the heart with cardiac tamponade. In two patients the pericardium contained about 50 c.c. of blood, and in the other two patients, 200 cubic centimeters. In three patients the rupture was in the left ventricle and in one patient, in the right. There were fresh infarcts in three patients, in one of whom there was also an aneurysmal bulge in the left ventricle at the site of an old infarct. In the fourth patient rupture appeared to be due to puncture of the left anterior descending artery from a needle wound.

It is concluded that there were three cases of spontaneous rupture among the eighty-four patients with fresh or organizing myocardial infarcts. The incidence is 3.6 per cent, which is less than the 8 per cent incidence reported in several series of cases,[36,159-162] although there is a wide range from 0 to 20 per cent.[144]

Ventricular Aneurysm.—The hearts of four soldiers presented ventricular aneurysms, all of the left ventricle. In one of these there was a fresh infarct in the interventricular septum and petechiae of the pericardium. In another there was rupture of the aneurysm, which apparently was the result of a fresh infarct. In a third patient the aneurysm was the product of an old infarct, and in the fourth patient the cause was an old infarct which left the ventricular wall 4 mm. thick and with a calcified rim. The incidence of aneurysm on the basis of 144 cases of gross infarction in this series is 3.5 per cent, whereas the incidence in the literature varies from 5 to 38 per cent for all ages.[144]

Atherosclerosis of the Aorta.—In 191 patients (42 per cent) there was some atherosclerosis of the aorta; in 103 of these there were a few plaques, confined usually to the root of the aorta, but sometimes involving also the abdominal portion; in eighty-five others there were more numerous plaques, involving both the thoracic and abdominal portions in the majority, and in three the degree of atherosclerosis was not given. In most of these patients the amount of atherosclerosis was slight or moderate in comparison to the degree of coronary sclerosis. In a few there was severe atherosclerosis of the aorta.

Lesions in Other Arteries.—The arteries and arterioles of the various organs were examined in order to determine whether there were significant lesions. The only organs in which there were noteworthy lesions were the kidneys, the brain, and the adrenal glands. Arteriosclerosis of the kidneys was found in only six patients, arteriolosclerosis in thirty-three. The arteriosclerosis was graded 1 plus (on a basis of 4) in all but one of the six patients, in whom it was 2 plus. The arteriolosclerosis was graded 1 plus in twenty-one, 2 plus in three, and 3 plus in six patients. Arteriolar necrosis of the kidneys was noted in five patients, in whom the arteriolosclerosis was graded 1 plus.

In eighteen patients the periadrenal arterioles were hypertrophied; 1 plus in fifteen, with necrosis in three of these, 2 plus in two, and 4 plus in one. Associated renal arteriosclerosis was present in only one-half of the eighteen patients.

Cerebral arteriosclerosis in a mild to moderate degree was observed in only ten patients. In a few patients in whom there was considerable atherosclerosis of the aorta, the first portion of the intercostal arteries, lumbar arteries, celiac artery, mesenteric artery, or renal arteries was also involved.

It is apparent that coronary artery sclerosis, in this series, is a specific disease of the coronary arteries and not a part of generalized arteriosclerosis.

Renal Lesions.—There were recent infarcts in five of the kidneys and scars of old infarcts in nine. A mild degree of glomerular sclerosis was found in twelve patients.

Lesions in the Brain.—Because of the suddenness of death in this group of young soldiers, the brain was examined in 253 patients. In 181 it was found to be normal; in fifty-two there was congestion or edema; in eleven, a mild to moderate degree of arteriosclerosis; in three, an area of hemorrhage; in three, an area of softening; and in three, a subarachnoid hemorrhage of small proportion.

Congestion of Organs.—There was no congestion of the lungs, liver, or kidneys in seventy-seven patients. In sixty-four patients the lungs alone were congested, in eleven the liver alone, in twenty-eight the kidneys alone, in thirty-eight the lungs and liver, in sixty-eight the lungs and kidneys, in nineteen the liver and kidneys, and in 140 the lungs, liver, and kidneys. In eight patients the presence or absence of congestion of these organs was not remarked upon and, hence, was probably absent.

ASSOCIATED PATHOLOGIC CONDITIONS

The following lists include the lesions other than cardiovascular found among the 450 autopsied cases.

RESPIRATORY

Pleuritis or pleural adhesions	58	Pulmonary infarct	7
Pulmonary tuberculosis, healed	34	Hydrothorax	7
Pulmonary emphysema	33	Tuberculous lymphadenopathy	2
Anthracosis	18	Congenital cyst of the lung	1
Pulmonary atelectasis	13	Empyema	1
Bronchopneumonia	12	Bronchopleural fistula	1
Bronchitis	8	Pulmonary thrombosis	1
Pulmonary tuberculosis, active	7	Tracheitis	1
Pulmonary fibrosis	7		

GASTROINTESTINAL

Gastritis	12	Polyp of the colon	1
Appendicitis, acute	3	Hemangioma of the duodenum	1
Meckel's diverticulum	3	Mucocele of the appendix	1
Diverticula of the colon	2	Appendicitis, healed	1
Duodenal ulcer	2	Peritonitis	1
Diverticulum of the ileum	1	Fibrosis of the pancreas	1

LIVER, GALLBLADDER, AND BILE DUCTS

Fatty changes in the liver	40
Cavernous hemangioma	6
Portal cirrhosis	3
Cholelithiasis	2
Cholecystitis, healed	2
Cholecystitis, acute	1
Cholangeitis	1
Tuberculosis of the liver	1
Fibroadenoma of the liver	1

GENITOURINARY

Sclerosis of the kidney	23	Aplasia of the kidney	1
Renal infarct, recent and old	14	Fibroma of the kidney	1
Hyperplasia of the prostate	9	Glomerulonephritis	1
Prostatitis	9	Pyelitis	1
Double ureter	4	Fetal lobulations, both kidneys	1
Atrophy of the testis	3	Diverticulum of the urinary bladder	1
Double pelvis	2	Prostatic urethritis	1
Cyst of the kidney	2	Prostatic calculi	1
Varicocele	2	Epididymitis	1
Prostatitis, healed	2	Absent left testis	1
Seminal vesiculitis	2	Malignant tumor of the testis	1
Renal calculus	2	Fibrosis of the testis	1
Adenoma of the kidney	1	Hydrocele	1
Pyelonephritis	1	Papillomas of the penis	1

ENDOCRINE GLANDS

Hyperplasia of the thymus	5
Persistent thymus	4
Involution of the thymus	1
Adenoma of the adrenal	3
Cyst of the adrenal	3
Hyperplasia of the adrenal	2
Pheochromocytoma	1
Periadrenal hemorrhage	1
Colloid goiter	1
Adenoma of the thyroid	1
Cyst of the thyroid	1
Cicatrix of the thyroid	1
Pituitary cyst	1

SPLEEN

Splenomegaly	21
Infarct	7
Tubercles, calcified	5
Accessory spleen	4
Acute splenic tumor	3
Fibrosis	1
Granulomas	1
Sarcoidosis	1

BRAIN

Leptomeningitis	4
Infarct	3
Subarachnoid hemorrhage	3
Embolus	1
Glioma, ependymal	1
Encephalomalacia	1
Calcification of the cerebral ganglia	1

MISCELLANEOUS

Thrombophlebitis	4
Hemorrhoids	2
Lipoma of the forearm	1
Lipoma of the buttocks	1
Lipoid depletion	1
Lymphadenitis	1

PROGNOSIS

Prognosis will be discussed in a subsequent paper in which various age groups will be compared.

SUMMARY AND CONCLUSIONS

World War II has afforded an opportunity to accumulate and study 866 cases of coronary artery disease in soldiers between the ages of 18 and 39 years, inclusive, 450 of whom were examined at necropsy. Two hundred three of these 866 men were under 30 years of age. Based on this figure, which is undoubtedly too small, the death rate from this cause per 100,000 men per year was less than 0.1 in age group 18 and 19 years, 1.0 in age group 25 to 29 years, 3.4 in age group 30 to 34 years, and 12.7 in age group 35 to 39 years. Therefore, deaths from coronary artery disease were more than thirty times as common in men 35 to 39 years of age as in those 20 to 24 years of age.

If these are assumed to be the rates for the entire population of the United States, it means that each year coronary artery disease will be the cause of death for twenty-four men 20 to 24 years of age, for fifty-four men 25 to 29 years age, for 183 men 30 to 34 years of age, and for 637 men 35 to 39 years of age. These figures are based on the estimated population of the United States for 1944 and 1945 published by the Bureau of the Census, Jan. 27, 1946.

There are sixty-three Negroes in the series. Since 10 per cent of the men in the entire Army were Negroes, this figure indicates that the rate of incidence of coronary artery disease among Negroes was approximately two-thirds that among Caucasians.

A study was made, both by means of questionnaires sent to the nearest of kin of the dead men and from histories obtained directly from those who survived, of many etiological factors, and these data were compared with similar information gathered from control groups. The only important conclusion that could be drawn concerned the effect of heredity, there being four times as many cases of cardiovascular disease in the immediate families of the survivors as in those of the control group.

Since many of the men appeared to be overweight at the time of death or of acute myocardial infarction, the factor of obesity was investigated. It was found that on induction the weight of these men corresponded to the average weight of all inductees and that during their Army careers they gained weight almost in the same relative degree as other soldiers. The weight gain of those who died paralleled that of the average soldier more closely than that of the survivors,

in whom there was a slight tendency to be overweight. Therefore, it appears that obesity cannot be said to be an etiological factor of any importance.

There was a slight though definite disposition toward hypertension in the group regarding both systolic and diastolic pressures, but more particularly the latter, and more notable in the survivors than in the men who died. However, only twenty-four men were considered clinically to be truly hypertensive. Nevertheless, in 27.9 per cent of the series systolic pressures were above 139 mm. Hg as compared with 8.9 per cent for an amputee control group, and in 19.1 per cent of the series diastolic pressures were above 89 mm. Hg as compared with 3.8 per cent for the control group.

The men in this series generally served for much shorter times than the men in the Army as a whole, which indicates that the rigors of Army life may have played a role in precipitating death. Death occurred in 45 per cent of the fatal cases during the first year of service and acute myocardial infarction in 34 per cent of the survivors within that period. There was a definite tendency for the older men to die earlier in their army careers.

The time of year and geographic location had no apparent influence in precipitating death.

The onset of the terminal illness or the "coronary attack" occurred relatively more often during strenuous activity than during mild and moderate activity and sleep. The proportion of attacks occurring during strenuous activity was more than twice as great as the proportion of the time spent in such activity, the proportion during mild and moderate activity was about equal to the proportion of time thus spent, and the proportion of men stricken while asleep was about one-third that of the proportion of time normally spent in sleep. The percentage of patients with an old or organizing thrombus in a coronary artery was considerably less among those who died while asleep than among those who died while engaged in waking activities. Conversely, the percentage of those with fresh thrombi was greater among the men who died in their sleep than in those who experienced the "attack" during activity.

Many men had had previous symptoms of cardiac disease, 9.3 per cent within three weeks of the "attack" ("premonitory" symptoms), 31.5 per cent with definite symptoms three weeks or more before the "attack," and 8.6 per cent with probable or possible symptoms of cardiac origin more than three weeks before the "attack." Therefore, about one-half of the men had symptoms before the onset of the "attack." Of the 450 men who died, fifty-seven had had anginoid attacks three weeks or more before death. These were mainly more or less isolated attacks of "coronary insufficiency" with pain, weakness, sweating, and sometimes dyspnea and other symptoms. Eight other men had had symptoms of partial or complete congestive failure. Seventy-three of the 400 survivors had had angina of effort, and in sixty-four other patients, there were attacks suggestive of "coronary insufficiency" and even coronary thrombosis, some with dypsnea as the main symptom. Twenty-eight of the men who died had had attacks that were suggestive but not typical of coronary insufficiency, most of them with symptoms referred to the abdomen. Twenty-seven of the survivors had had symptoms of similar nature, but dyspnea on exertion was noted more often than

abdominal complaints. The "prodromal symptoms" that were present in sixty men within three weeks of the "attack" were, in general, similar to the attacks that occurred in other men three weeks or more before the "attack." Several men had been hospitalized previously for cardiac complaints. The diagnosis of cardiac disease was made in some of these but not in others.

There was no correlation between the presence or absence of a previous cardiac history and the pathologic changes found, although men with previous cardiac symptoms tended to have myocardial infarcts or myocardial scars more frequently.

Of the 450 patients who died, death occurred within twenty-four hours of the onset of symptoms in 375 (83.3 per cent). Age did not appear to be related to the duration of the terminal illness. Duration of illness, on the whole, was also not related to the lesion found. However, the longer a man lived the more likely he was to have myocardial infarction whether or not he had a previous cardiac history.

Pain was present in 98.4 per cent of the men, being the primary or first symptom in 575, but ensuing rapidly in the other fifty-seven of the 642 patients in whom a history could be elicited. Manifestations of shock were the next most common symptom at the onset, occurring in 17 per cent, but nearly eight times more often among the men who died than among those who lived. Dyspnea occurred soon after the onset in 58 per cent, nausea, vomiting, or both in 36 per cent, and nervous manifestations in 18.5 per cent. Unconsciousness occurred in 11 per cent, indigestion in 7 per cent, dizziness in 6 per cent, and convulsions in 4 per cent. Diarrhea developed during the "attack" in fourteen patients. Several symptoms occurred almost simultaneously from the start in many instances. Congestive failure occurred during the "attack" in ten men, and hemiplegia, in five.

In general, the pain was similar to that well known for coronary artery disease. Radiation occurred from the primary site in nearly 67 per cent of the cases. A feature of great interest was exacerbation of the pain on deep inspiration in 10 per cent of the survivors. None of these men had pericardial or pleural friction rubs.

Of the fifty-four men who died during hospitalization, thirteen developed congestive failure, embolization occurred in five, and convulsions occurred in six. Pain recurred in forty-five of these men and was present terminally in twenty-two.

Of the 400 survivors, cardiac enlargement was thought to be present in sixteen. Poor heart sounds were noted in seventy-two men. Premature ventricular contractions occurred in fifty-seven patients, paroxysmal auricular tachycardia in two, auricular fibrillation in two, and auricular flutter in one. These arrhythmias were all transient. Systolic murmurs were heard in thirty-three men and diastolic murmurs, in two. These also were transient. Gallop rhythm was noted in twenty patients and it persisted in three. Signs of pulmonary congestion occurred in forty-one patients during the "attack." Transient pericardial friction rub was heard in twenty-eight patients.

The behavior of the blood pressure among the survivors during the attack was interesting. In practically 20 per cent of the men there was a rise in both systolic and diastolic pressures in the initial stage of the "attack." Both systolic and diastolic pressures dropped in only 14 per cent of the cases. In 70 per cent of the patients the blood pressure remained normal or returned to normal within twenty-four hours after the initial period of hospitalization and continued to be normal throughout the period of observation in the hospital. In the 22 per cent of the patients in whom there was either an elevation or lowering of the pressures during the acute "attack," normal levels were reached forty-eight hours or more after the onset of the "attack." In 4 per cent of the patients the pressure was constantly elevated during convalescence, and in 4 per cent it was constantly low during convalescence.

The electrocardiograms made in some of the men who died showed some discrepancies with the lesions found, but in general, they agreed. Serial electrocardiograms were made in all who survived. Anterior infarction was indicated in 176 patients, posterior infarction in 113, some form of lateral infarction in 56 patients; nonlocalizing electrocardiographic changes were present in fifty-five.

Among 274 patients with adequate data, elevation of temperature, leucocytosis, and increased sedimentation rate occurred in 58 per cent: two of these three abnormalities were present in 28 per cent; and one abnormality existed in 12 per cent. In only 2 per cent were the temperature, white blood cell count, and sedimentation rate normal. In general, there was parallelism of the three findings.

The clinical course of the survivors showed asymptomatic recovery in 57 per cent, recurrence of pain in 25 per cent, congestive failure in 2 per cent, pulmonary congestion in 4 per cent, dyspnea without râles in 5 per cent, pulmonary infarction in more than 1 per cent, and pleural effusion in almost 1 per cent.

Diagnostic accuracy was 58 per cent in the men who died and 71 per cent on first examination in the survivors.

Seventeen of the 400 have survived another acute myocardial infarction and twenty-eight have developed congestive failure. Dyspnea on exertion has been the most prominent symptom following healing of the infarct, with angina of effort running a close second (62 and 52 per cent respectively). Tiredness has been fairly common. Fifty per cent of 361 men adequately followed up have returned to full-time employment; 41 per cent have not been able to work at all.

The Negroes were studied separately and were found to present clinical and pathologic features in every way similar to the Caucasians.

All of the 450 hearts examined at necropsy had advanced arteriosclerosis of the coronary arteries. There were 114 with gross myocardial infarction, fourteen with two infarcts, and two with three infarcts. In eight hearts no complete occlusion of any artery was found; in twenty-seven hearts there was sclerotic occlusion alone, in fifty-five, thrombotic occlusion alone, and in twenty-four, both sclerotic and thrombotic occlusion. Of the 336 patients without gross myocardial infarction, there were thirty-eight without complete occlusion of any artery, 148 with sclerotic occlusion alone, 117 with thrombotic occlusion alone, and thirty-three with both sclerotic and thrombotic occlusion.

The lesions of the coronary arteries were similar to those of the coronary arteries in cases of coronary artery sclerosis in patients over 40 years of age, but they were found to be more advanced in age as the men advanced in years. The atheromatous plaque was the prominent lesion of the arteries microscopically. Hemorrhage in the plaque was found in 12 per cent.

Fifty-two per cent of the hearts were hypertrophied, 16 per cent moderately or greatly so. There were no more than sixteen patients with hypertension at the time of the fatal "attack" and only six patients with valvular disease in whom the hypertrophy could be accounted for on any other basis than the effects of coronary artery disease. Myocardial infarction and myocardial scars were the most prominent factors associated with hypertrophy, in addition to the coronary arteriosclerosis. Men with the larger hearts tended to live longer.

Cardiac dilatation of moderate degree was found in twenty-four patients and of severe degree in six patients.

The myocardial infarcts, numbering 130 found on gross examination and twenty-three on microscopic study, were located in the left ventricle and/or interventricular septum in all but seven patients, in whom they were in the posterior wall of the right ventricle. They were in the posterior wall of the left ventricle in twelve patients and in the lateral wall of that ventricle in five patients. The gross infarcts were fresh in sixty-eight patients, organizing in twenty-two, old in thirty-four, and of unstated age in six. In sixteen patients there were two gross infarcts. They varied in size from microscopic to more than 6 cm. in diameter.

Scars were present in the myocardium in 262 patients.

In forty-six patients the coronary arteries were sclerotic but their lumina were not occluded. In 232 men there was practically complete sclerotic occlusion in some part or parts of one or more coronary arteries; in 192, in the left anterior descending branch, in fifty-nine, in the right coronary artery, and in sixty, in the left circumflex branch. Sclerotic occlusion was present in two or all three of the arteries in sixty patients. In 229 patients there was thrombotic occlusion, recent, organizing, or old, in some part or parts of one or more coronary arteries; in the left anterior descending branch in 174, in the right coronary artery in forty-nine, in the left circumflex in twenty-eight, and in two or all three of the arteries in nineteen patients. The great majority of the occlusions were in the proximal one-third of the arteries. There were fresh thrombi in 156 men, organizing thrombi in nineteen, old thrombi in twenty, both old and fresh thrombi in twelve, and thrombi of unstated age in twenty-two patients.

Mural thrombi were present in forty-three patients (38 per cent of the 144 with gross myocardial infarcts).

Rheumatic valvular disease was present in ten patients and syphilitic aortitis in one patient.

In twelve patients there was focal fibrinous pericarditis and in one patient, diffuse fibrinous pericarditis. Patches of old fibrous pericarditis were found in nine patients and old total obliterative pericarditis in one patient.

There were four examples of rupture of the heart with cardiac tamponade. One of these may have been the result of puncture of a coronary artery by a

needle inserted for the purpose of resuscitation. Ventricular aneurysm was found in four patients.

In 191 patients there was atherosclerosis of the aorta, but in 103 the lesions were comparatively insignificant. Important sclerosis of other arteries was numerically insignificant.

There was some congestion of the lungs, liver, and/or kidneys in all but seventy-seven patients.

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A CLINICAL EVALUATION OF VERATRUM VIRIDE IN THE TREATMENT OF ESSENTIAL HYPERTENSION

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AS A therapeutic agent veratrum viride fell into disrepute many years ago. Formerly it was used to "soften the pulse" and lower the body temperature in infectious fevers. These effects were produced by administration of the drug in doses sufficient to cause collapse.[1] The tinctures in use at that time were so poorly standardized that the effective dose could not be calculated in advance. Because it slowed the pulse and lowered the blood pressure, often to a state of collapse, veratrum was thought to be a "cardiac depressant." For these various reasons the drug has been condemned in textbooks of pharmacology.[1-3] Actually, however, veratrum viride was cast into discard[3] before its pharmacologic effects on the circulatory system had been elucidated.[4]

A review of the more recent pharmacologic data concerning the veratrum alkaloids indicates that a significant reduction in arterial pressure occurs with doses below the toxic level.[5] The fall in arterial pressure apparently is associated with peripheral vasodilatation rather than with depression in cardiac output.[5,6]

Much pharmacologic evidence has accumulated to show that the circulatory effects of veratrum are mediated through nervous pathways. The reduction in blood pressure and cardiac rate observed with subtoxic doses in animals may be abolished by section or cold block of the vagus nerves.[5] Amann and Schaefer[7] have recently demonstrated that various afferent fibers are present in the cardiac branches of the vagus nerves which carry bursts of electrical activity in phase with the heart beat. These afferent nerves can be caused to fire off continuously by the injection of veratrine. Dawes[8] has confirmed in dogs and cats the fact that the reflex fall in blood pressure and heart rate following the injection of veratridine originates from the afferent vagus nerve endings in the myocardium of the left ventricle and in the lungs. This interesting laboratory evidence suggests that there is a vasodepressor mechanism mediated through the afferent vagus nerve endings in the thorax which can be excited to continuous activity by the veratrum alkaloids.

The effects of veratrum in the treatment of essential hypertension have not been extensively studied. Collins[9] observed the results of a single dose of

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the tincture in hypertensive patients. He concluded that definite and often striking reductions in blood pressure could occur with the use of subtoxic doses, but he made no attempt to treat his patients over long periods of time. The hypotensive effects were confirmed by Wedd[10] and by Hewlett and associates.[11] Hite[12] treated hypertensive patients continuously for eight months and concluded that veratrum viride is a valuable therapeutic agent in this disease. The drug has been used for many years in the treatment of eclampsia.[13-15] However, the available pharmacologic and clinical data suggested to us the need for re-evaluation of veratrum viride with particular reference to its use as a therapeutic agent in the treatment of essential hypertension. This communication reports the results of a clinical trial of this drug in a series of forty hypertensive patients. Experimental studies of the hemodynamic effects of veratrum, especially upon cardiac output, peripheral resistance, hepatic blood flow, renal clearances, sympathetic reflexes, limb and digit plethysmography, and skin temperatures will be reported elsewhere.[6]

SUBJECTS AND METHODS

The subjects were a heterogeneous group of forty patients with essential hypertension who were treated on the wards and in the Outpatient Department of the Massachusetts Memorial Hospitals. The period of observation under veratrum treatment varied from several weeks to as long as thirteen months. Thirty-one of the patients received the drug for periods longer than two months. Prior to treatment all patients were observed under routine symptomatic therapy including rest, sedation, and the usual forms of psychotherapy. Nine patients had previously received treatment with potassium thiocyanate and eight had received pentaquine.[16] Fifteen of the patients received treatment with a salt-free diet or the "rice diet." In all except the special instances described below, previous dietotherapy and drug therapy were withdrawn before veratrum was administered.

The blood pressure was measured with a mercury manometer with the patient in both the erect and the supine positions after he had rested for at least fifteen minutes in the supine position. The pulse rate was counted at the wrist or the cardiac apex.

The veratrum preparation used was the whole powdered mixture of alkaloids prepared in tablets. This preparation, which in our experience has had a fairly uniform potency, was biologically standardized so that each tablet contained 10 "Craw units."*

RESULTS

Therapeutic and Toxic Dosage.—The therapeutic dose of veratrum viride varied from 10 to 40 Craw units in those patients who responded to the drug. Increasing the dosage beyond this point resulted in further reduction of blood pressure, but inevitably led to toxic reactions. The margin between the therapeutic

*The preparation of veratrum viride which bears the trade name of "Vertavis" was generously supplied by Irwin, Neisler, and Co., Decatur, Ill. A Craw unit is defined as the amount which causes cardiac arrest in the crustacean, *Daphnia magna*.

and toxic doses usually was no greater than 10 Craw units. For any given individual the effective dose could be determined only by trial with gradually increasing doses. The therapeutic dose bore no relation to the surface area of the patient or the severity and duration of the disease.

If the effective dose was greater than 10 Craw units, ingestion of the total dose at one time frequently resulted in side reactions, particularly nausea and vomiting. However, by subdividing the total effective dose so that no more than 10 Craw units were administered at hourly intervals, these side reactions were reduced considerably.

Time-Dose Relationships.—Although there was great individual variation in the size of the effective dose (herein defined as that dose which resulted in a reduction of at least 20 mm. in systolic and 15 mm. in diastolic blood pressure), the onset and duration of the hypotensive response was quite uniform in different patients. When an effective dose was administered, the hypotensive response began in one or two hours, reached a maximum in four to six hours, and ended in approximately twelve to fourteen hours. An example of this sequence is provided by a patient admitted to the hospital because of hypertensive crisis with encephalopathy.

CASE 1.—J. Mc., a 51-year-old white man, was admitted to the Evans Memorial Hospital on June 16, 1947. On the day of admission he was seen in the outpatient department where he was found to be mentally confused. The blood pressure, which had previously been 240/130, had risen to 270/170. In the hospital he was observed to be disoriented as to time and place; he exhibited echolalia, mixed visual and verbal agnosia, and acoustic agnosia. Neurological examination revealed no localizing signs. Venesection was performed with the removal of 500 ml. of blood without significant reduction of blood pressure.

Veratrum viride was then administered in amounts of 10 Craw units every hour for three doses followed by 10 Craw units every other hour for three doses (Fig. 1). Eight hours after veratrum was begun, the blood pressure had fallen to 150/60, and the pulse rate, from 125 to 80 per minute. Eight hours after veratrum had been discontinued, the blood pressure began to rise again, stabilizing at 230/140 sixteen hours after the last dose of the drug. The pulse rate rose to 100 per minute. During the period of hypotension there was gradual clearing of the sensorium so that twenty-four hours after admission the patient was oriented as to time and place and was able to carry on an intelligent conversation.

If the dosage intervals were not separated by at least eight hours, successive doses soon resulted in the appearance of toxic reactions. The toxic effects resulting from cumulative overdosage may be illustrated by the following case.

CASE 2.—L. S., a 39-year-old white woman, with known hypertension for eight years, complained of dyspnea, orthopnea, and dependent edema for five months prior to admission to the hospital. After two weeks of hospital treatment with digitalis and mercurial diuretics, the signs of cardiac failure cleared. The blood pressure at this time was 210/135. Treatment with veratrum was begun and the dosage was gradually increased to 90 Craw units per day administered in divided doses of 30 Craw units at 10:00 A.M., 2:00 P.M., and 6:00 P.M. At 6:30 P.M. the patient experienced numbness in the feet, hands, and lips, blurred vision, increased sweating, soon followed by nausea with severe vomiting, excess salivation, and collapse in the upright position. The blood pressure at this time was 120/80 and the pulse rate, 54 (Fig. 2). These symptoms gradually abated during the next three hours and had completely disappeared in sixteen hours.

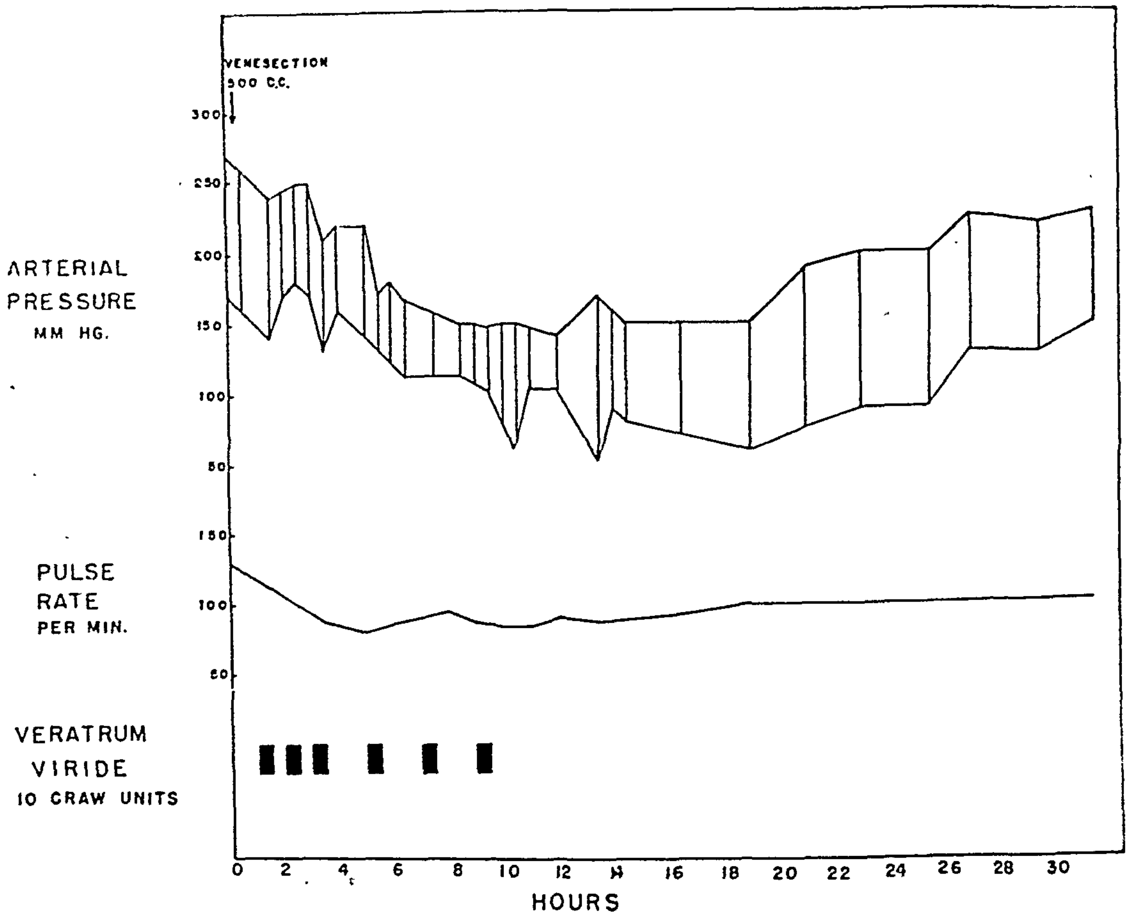

Fig. 1.—The duration of the hypotensive response to orally administered veratrum viride as shown in Patient J. Mc. (Case 1).

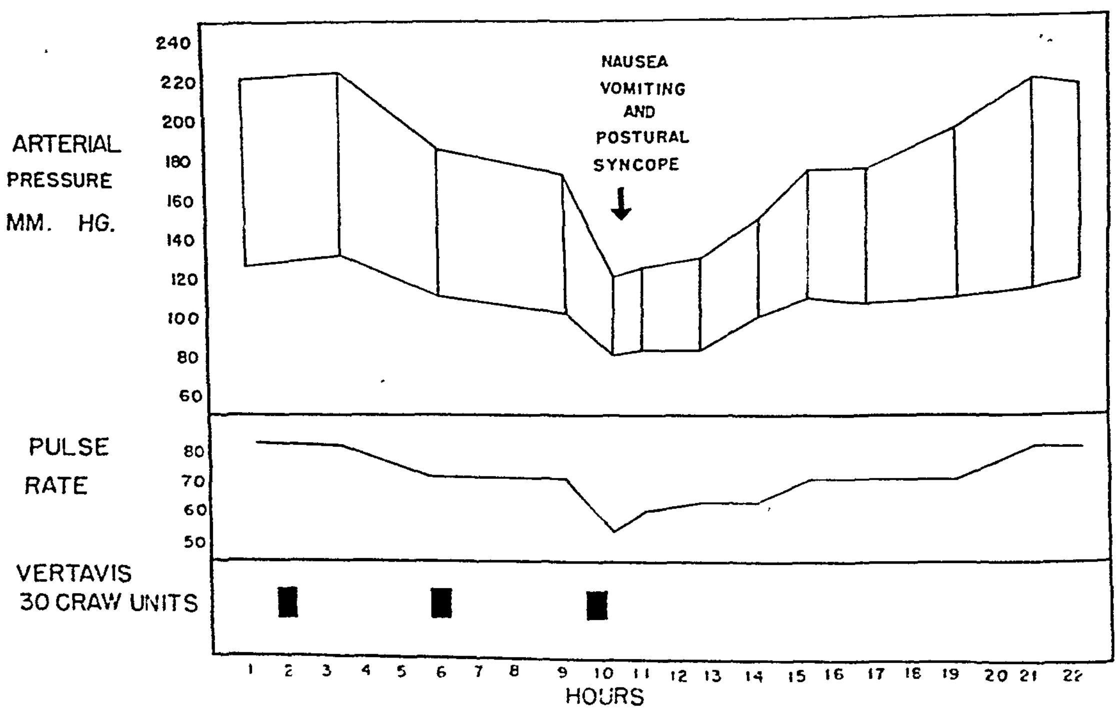

Fig. 2.—The toxic reaction resulting from the effects of cumulative overdosage when veratrum was administered at intervals of four hours (Case 2).

This patient received three doses of 30 Craw units at four-hour intervals. Since veratrum is present and active in the body for twelve hours, at 6:30 P. M. she suffered the toxic reactions resulting from a cumulative dose of 90 Craw units. Such severe reactions were fairly frequent in the early phase of the investigation, but were almost completely eliminated when the effective doses were separated by a twelve-hour interval.

Therapeutic Results.—

Hospitalized Cases: In order to evaluate the hypotensive activity of veratrum viride under controlled conditions, the drug was administered to six hospitalized patients who had shown little hypotensive response to other types of medical treatment, including hospital bed rest (Table I). During the control period three patients received sedation in the form of phenobarbital (30 mg. three times per day), two patients received the Kempner rice diet[17] for ten days and two weeks, respectively, and one patient was given a "salt-free" diet supplemented with mercupurin (2.0 c.c. intravenously twice per week). The period of control observations in the hospital varied from ten to thirty days prior to the institution of veratrum treatment.

In each case all blood pressures were recorded by the same individual. The blood pressure taken initially was not recorded and the patient was then allowed to rest for thirty minutes. Following this initial period, the blood pressure and pulse rate were recorded once a minute for five minutes in the supine position, followed immediately by five minutes in the erect position, and then a final five minutes in the supine position. In the control period the lowest values for systolic pressure, diastolic pressure, and pulse rate were selected to compare with the highest values recorded in the period after treatment with veratrum viride.

Although all of these patients were hospitalized throughout the study, they were not in bed at all times, except four patients whose blood pressures were recorded after forty-eight hours or more of complete rest in bed. In every case, after treatment with veratrum was begun, patients were allowed to be up and about the ward. The previous regimen of treatment was continued, the only change being the addition of veratrum viride.

The results listed in Table I indicate that in five of the six cases a significant reduction in blood pressure occurred following therapeutic doses of veratrum viride. In one case (Patient L. S.) significant hypotension did not occur after therapeutic doses, but developed only after toxic doses. In the four cases in which the drug was withdrawn, there was a prompt return of blood pressure to pretreatment levels.

Outpatient Cases: The foregoing results seemed sufficiently significant to warrant further clinical trial of veratrum viride over longer periods of time in ambulatory patients. The latter data are summarized in Table II. Of the thirty-four patients studied, all except four exhibited a significant reduction in blood pressure when compared with the values obtained during the control period. However, the results were seldom as striking as after acute administration of the drug in the hospital, and in only one case did the blood pressure fall to normal.

TABLE I. THE HYPOTENSIVE EFFECT OF VERATRUM VIRIDE COMPARED WITH THAT OF OTHER FORMS OF THERAPY IN HOSPITALIZED PATIENTS

PATIENT	SEX	AGE (YEARS)	KNOWN DURATION OF HYPERTENSION (YEARS)	TIME AFTER ADMISSION TO HOSPITAL (DAYS)	TREATMENT	BLOOD PRESSURE LYING	BLOOD PRESSURE STANDING	PULSE RATE PER MINUTE
C. S.	M	43	10	1	0	234/160	253/172	90
				3	Complete bed rest 48 hrs.	232/146	233/160	85
				10	0	225/130	210/150	92
				12	Vertavis, 30 Craw units b.i.d.	190/110	190/130	68
				15	Vertavis discontinued	225/130	222/154	84
R. Mc.	M	38	1	1	0	190/140	185/140	72
				14	Low-salt diet; mercurials	170/135	170/140	68
				16	Vertavis, 10 Craw units daily	142/100	120/90	58
M. S.	F	48	6	1	0	218/140	215/152	75
				3	Complete bed rest 48 hrs.	210/130	220/145	75
				30	Strict rice diet 10 days	190/130	190/150	82
				34	Vertavis, 40 Craw units, single dose	155/105	160/130	90
				43	Vertavis discontinued	220/138	215/144	82
				48	Vertavis, 30 Craw units b.i.d.	175/115	180/125	80

L. S.	F	43	8	1	0	218/160	225/160	115
				14	Phenobarbital, 30 mg. t.i.d.	215/120	210/140	80
				18	Vertavis, 90 Craw units (over 8-hr. period)	150/80*		64
				20	0	220/120	210/135	82
				21	Vertavis, 40 Craw units b.i.d.	200/120	200/120	84
C. B.	M	43	2	1	0	220/140	240/160	85
				3	Complete bed rest 48 hrs.	232/145	222/158	82
				10	Phenobarbital, 30 mg. t.i.d.	240/140	230/155	80
				14	Vertavis, 30 Craw units b.i.d.	195/130	160/130	60
				24	Vertavis discontinued	220/130	230/150	82
P. P.	M	41	5	1	0	240/145	235/160	70
				4	Complete bed rest 72 hrs.	235/140	215/160	65
				18	Strict rice diet 2 weeks	240/162	208/170	76
				23	Vertavis, 30 Craw units b.i.d.	180/135	146/126	62
				27	Vertavis discontinued 24 hrs.	230/138	220/155	74
				33	Vertavis, 30 Craw units b.i.d.	146/96	130/104	50

*Collapse, nausea, and vomiting.

Except for the periods of complete bed rest noted, the patients were up and about the ward. Prior to veratrum, different types of medical therapy were substituted as indicated. When treatment with veratrum was started, the immediately preceding medical therapy was continued and was maintained even after veratrum was discontinued.

Table II. Results of Therapy With Veratrum Viride in Thirty-four Ambulatory Hypertensive Patients Treated for Periods of 1 to 13 Months

PATIENT	SEX	AGE	KNOWN DURATION OF HYPERTENSION (YEARS)	CONTROL PERIOD						AFTER VERATRUM VIRIDE						
				DURATION OF OBSERVATION (MONTHS)	NUMBER OF VISITS	MEAN OF BLOOD PRESSURE RECORDINGS—MM. HG		MEAN PULSE RATE SUPINE PER MINUTE	CRAW UNITS PER DAY	DURATION OF OBSERVATION (MONTHS)	NUMBER OF VISITS	MEAN OF BLOOD PRESSURE RECORDINGS—MM. HG		MEAN PULSE RATE SUPINE PER MINUTE	TOXIC REACTIONS	SYMPTOMATIC IMPROVEMENT
						SUPINE	ERECT					SUPINE	ERECT			
C. B.	F	52	10	2 weeks*	14	235/140	220/140	76	50	13	46	200/125	165/110	78	0	++
R. Mc.	M	38	1	2 weeks*	28	170/140	170/140	60	30	10	12	160/100	150/110	54	0	+++
C. S.	M	45	8	2 weeks*	14	225/140	225/145	80	60	12	14	210/125	205/125	68	+	+++
G. P.	M	48	7	12	6	190/120	190/125	95	50	13	18	170/110	155/110	68	0	++
P. E.	F	44	13	1	3	220/135	200/140	80	60	4	9	170/100	145/110	76	+	+++
J. F.	M	56	2	1	3	240/100	210/105	82	80	6	8	200/85	170/95	64	+	0
V. F.	F	36	13	8	6	255/150	265/170	108	80	2	5	245/160	245/160	103	0	+
C. F.	M	52	1	4	7	210/120	210/120	76	60	9	20	180/105	170/110	76	0	++
R. K.	M	52	10	1	3	200/115	210/135	72	30	2	4	180/100	160/100	68	0	0
J. Mc.	M	66	6	2	4	240/145	235/150	104	50	6	9	210/130	190/130	90	0	+++
I. S.	M	46	6	2 weeks*	60	170/110	180/130	84	70	2	4	150/110	150/120	76	0	+
E. S.	F	50	21	2	4	240/140	195/150	84	70	6	14	210/120	180/120	72	+	+
E. A.	F	54	4	3 days*	10	240/150	220/160	100	50	10	12	225/130	210/140	90	0	++
N. F.	M	34	0	6	5	170/125	155/125	72	40	2	4	150/100	140/110	65	+	+

F. G.	F	45	28	3	4	255/120		78	30	6	8	240/115		70	0	+++
P. H.	F	47	0.2	1	4	230/130	180/130	76	30	3	4	180/100	160/110	0	+	++
J. C.	M	51	0.3	10	20	210/145	180/140	68	40	2	6	195/125	160/115	68	+	+
J. D.	M	38	7	2	4	180/120	160/130	88	40	2	5	160/105	160/105	82	0	0
E. S.	F	45	0	1 week*	24	225/140	190/130	90	60	2	4	185/120	170/115	54	0	+++
I. P.	M	30	6	3	4	160/120	170/130	80	50	3	3	145/95	135/110	76	0	+
I. S.	M	57	6	7	4	170/90	160/90	74	40	1	3	135/75	145/85	70	0	0
A. C.	M	45	0.5	6	8	180/110	170/100		70	1	3	145/90	140/90	72	0	+++
M. C.	F	42	6	8	5	185/120		84	20	4	5	160/90		84	0	+++
C. D.	F	43	1	6	10	215/130	195/125	92	50	2	6	185/120	170/125	94	0	++
W. G.	M	49	2	1	4	190/130	190/140	100	50	4	4	170/110	180/130	80	0	+++
M. A.	M	41	7	1 week*	7	170/115	165/120	110	50	10	12	170/120	170/120	94	0	++
L. Mc.	F	51	12	12	6	215/110	210/120	65	30	3	8	165/95	150/100	58	+	0
F. D.	M	30	0.6	4 weeks*	28	180/120		76	60	2	10	130/85	125/90	70	+	+
M. A.	M	41	7	5	8	210/130	200/140	80	60	4	6	190/130	170/120	80	+	+
N. C.	M	54	0.4	3	6	190/110	180/120	98	10	4	8	190/110	140/100	68	+	+++
L. B.	F	46	5	1	4	190/115	210/120	80	60	3	10	185/120	165/115	72	+	+
E. H.	F	57	0.5	2	4	190/115	180/120	112	50	1	4	165/105	133/110	120	0	++
W. B.	M	46	0.5	1	3	200/115	190/120	80	30	1	2	155/105	160/110	76	0	+
M. D.	M	43	2	3	5	180/120	175/125	76	50	2	4	150/95	155/105	64	+	+

*Observations made in the hospital.

Twenty-seven of the thirty-four patients (79 per cent) expressed subjective improvement. Three patients felt worse while taking the drug, and the remaining four patients either had no complaints prior to or during treatment or noted no change in their symptoms. The most remarkable improvement occurred in those patients who complained of exertional dyspnea and palpitation. Many patients noted a general improvement in physical and mental well-being which often was associated with a definite hypotensive response.

In several of the patients who had been taking veratrum for periods longer than one month, reductions in the cardiac silhouette by roentgenography as well as changes toward normal in the electrocardiogram were demonstrated (Figs. 3 and 5). There was no evidence of change in renal function as measured by concentration tests, routine urinalysis, and the excretion of phenolsulfonphthalein.

Following treatment with veratrum viride, a remarkable dilatation of the retinal arterioles has been reported in a patient with eclampsia.[18] A similar relaxation of arteriolar spasm was occasionally observed in the optic fundi in this series of patients with essential hypertension. In one patient, in whom there was generalized constriction of all the branches of the ophthalmic artery with numerous local spasms in the nasal branches, the caliber of the vessels reverted entirely to normal during the period of hypotension. Such marked changes were seen only in those patients who exhibited great reductions in blood pressure.

The most interesting results with veratrum were obtained in the so-called "resistant" types of cases. Patients with high diastolic and/or wide pulse pressure, those with long-standing hypertension, and those with cardiac failure or repeated cerebrovascular accidents responded as well as the early mild cases. Sex and age did not materially alter the response to the drug. A number of the patients in this series, although far from cured, were able to return to work from a life of semi-invalidism. The following cases serve as illustrative examples:

CASE 3.—C. S., a 45-year-old white man, had a history of two cerebrovascular accidents in the fifteen months prior to admission to the hospital. On the advice of his physician he retired from his work as manager of a bakery. In the hospital he was found to have cardiac enlargement, Grade III arteriosclerotic and Grade II hypertensive changes in the eye grounds, and impaired renal function without nitrogen retention. After two weeks of rest in the hospital, during which time he received a salt-free diet, the blood pressure was 240/130.

Treatment was begun with veratrum and the dosage was increased to 30 Craw units every twelve hours. The blood pressure fell immediately to 190/110. He was discharged from the hospital feeling considerably improved and within a month had returned to work. During the past eight months his blood pressure was never higher than 210/120 on repeated outpatient visits and usually was well below this figure.

He was readmitted to the hospital for further study seven months after beginning treatment with veratrum. Re-examination of the heart by roentgenography revealed diminution in cardiac size. The electrocardiogram showed changes toward normal since the examination seven months previously (Fig. 3).

After the second hospital day the medication was discontinued for fifty-four hours. It will be noted in Fig. 4 that soon after the medication was withdrawn the blood pressure gradually rose from a general level of 185/110 to a level of 230/120. With the resuming of veratrum therapy the blood pressure returned to the lower level. It is of interest that when the drug was discontinued the patient complained of headache and palpitation which again disappeared after treatment was resumed.

The following case demonstrates the effect of veratrum in a patient with cardiac failure secondary to hypertension.

CASE 4.—R. Mc., a 38-year-old resort hotel manager, noted the onset of exertional dyspnea, substernal oppression, and occasional attacks of paroxysmal nocturnal dyspnea eight months prior to admission to the hospital. Five months before admission he consulted his physician who found his blood pressure to be 220/140. He was advised to stop work and was given digitoxin, 0.2 mg. per day, nitroglycerin, and occasional injections of mercurial diuretics. He failed to improve, however, and was admitted to the hospital.

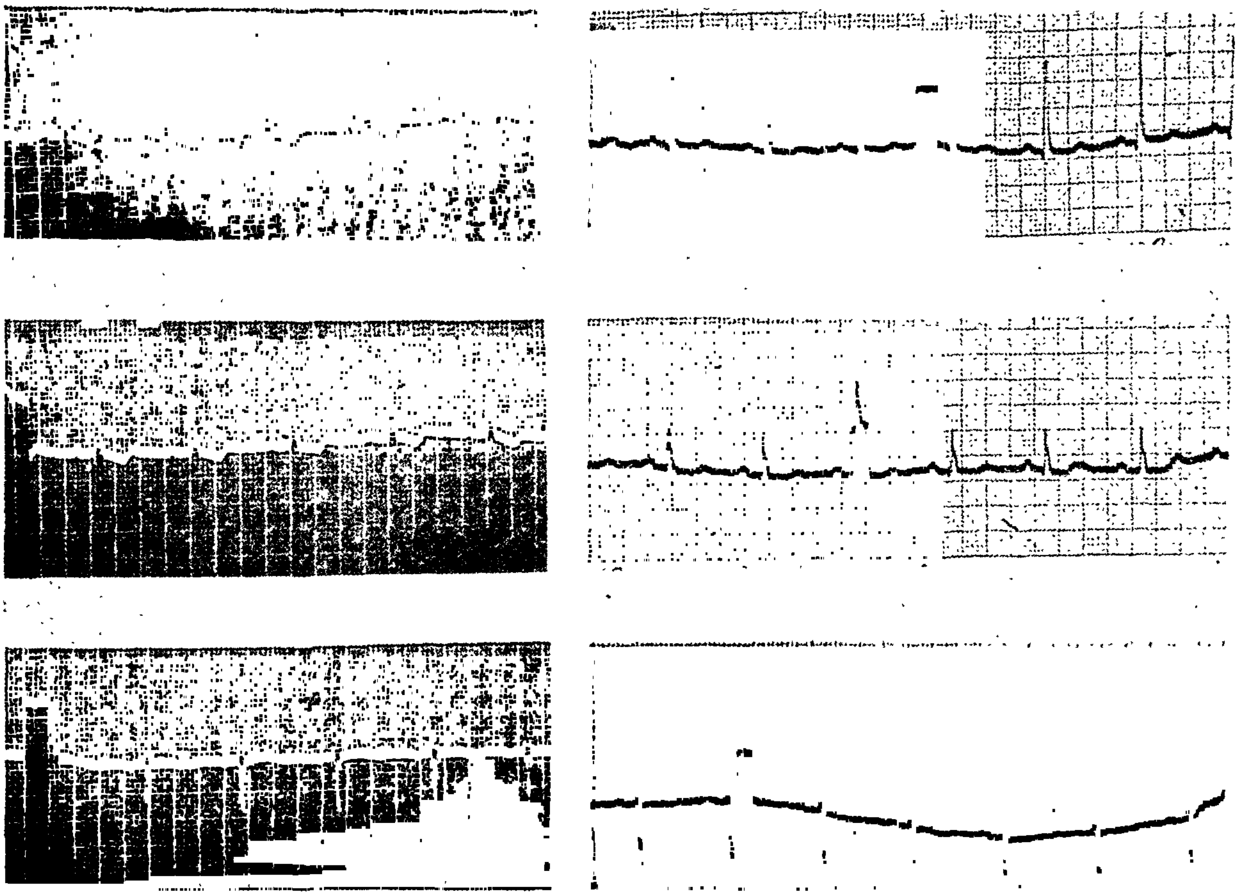

FIG. 3.—Electrocardiograms of Patient C. S. (Case 3). The three limb leads are shown from above downward. The electrocardiographic tracing on the left was taken prior to treatment and that on the right was taken after seven months of continuous treatment with veratrum viride. Inverted T waves in Leads I and II have now become upright.

Physical examination revealed the signs of cardiac failure including edema of the lower extremities. There was narrowing and tortuosity of the retinal arterioles. The urine contained 3 plus albumin and concentrated to 1.018. Phenolsulfonphthalein excretion was reduced. The electrocardiogram was interpreted as showing digitalis effects and left ventricular strain. There was cardiac enlargement and pulmonary congestion by roentgen ray.

The blood pressure, which was 190/140 on admission, fell to 170/120 several days after admission. The edema of the legs cleared after diuresis with mercupurin. Veratrum therapy was begun at a dosage level of 10 Craw units twice per day. The blood pressure in the supine position fell to 140/100, and in the standing position, to 120/90. He was discharged from the hospital on this dosage plus digitoxin 0.2 mg. daily, and in two months returned to work.

During the past seven months since discharge, the blood pressure ranged between 180/110 in the supine and 160/110 in the erect position. He experienced no further attacks of dyspnea or angina and has required no further treatment with either mercurial diuretics or nitroglycerin.

Roentgenographic examination of the heart six months after veratrum was begun showed reduction in cardiac size and clearing of congestive changes (Fig. 5). It was necessary gradually to increase the dosage of veratrum to 30 Craw units every twelve hours in order to maintain the hypotensive response. The patient was employed through a strenuous summer season with no evidence of cardiac failure. On one occasion veratrum was withdrawn for a period of five days. This was followed by a rise in blood pressure from 180/110 to 210/130 and an increase in pulse rate from 64 to 100 per minute. During this period the patient noted palpitation which promptly disappeared as soon as the drug was resumed.

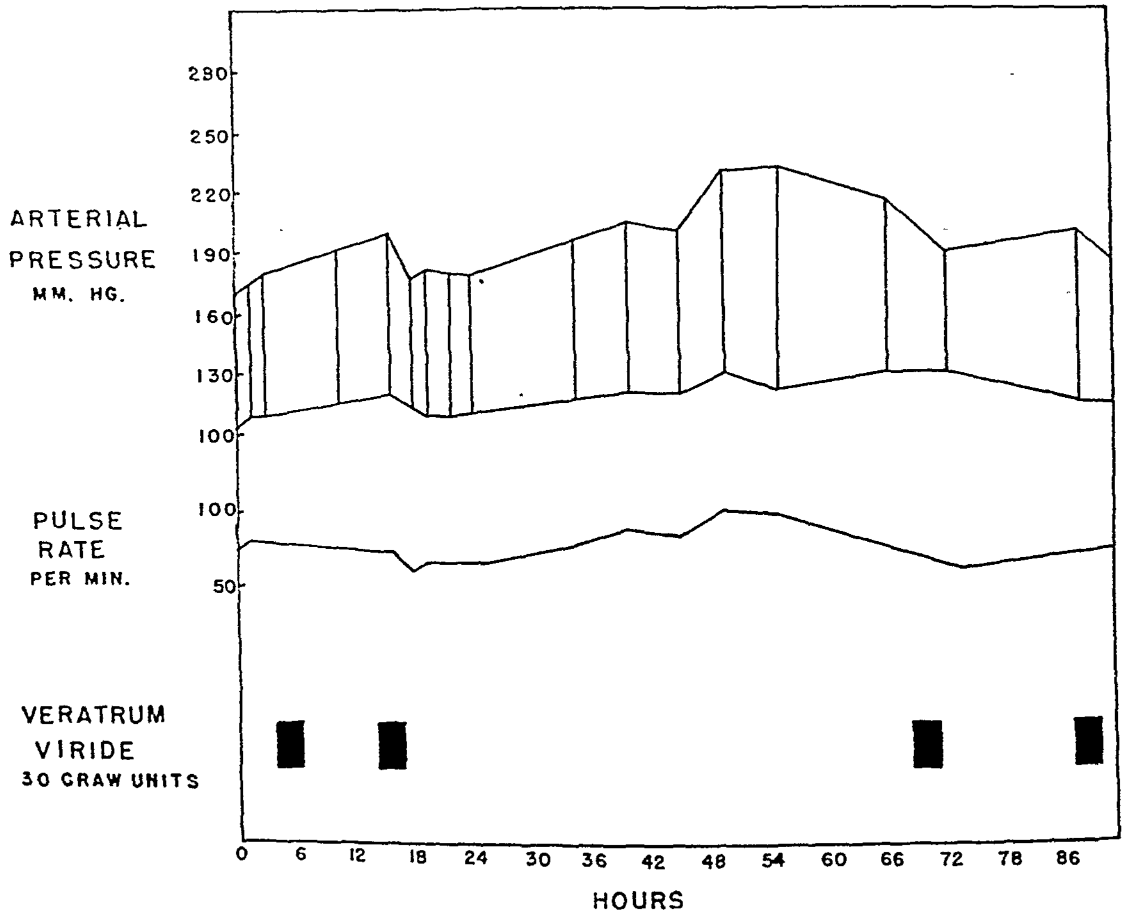

Fig. 4.—The effect of withdrawing medication in Patient C. S. (Case 3) who had been treated with veratrum viride continuously for seven months. Withdrawal of the drug was followed by elevation of the blood pressure and pulse rate which again fell following reinstitution of treatment.

Veratrum viride was also found to enhance the effectiveness of sympathectomy and of dietotherapy. The following case illustrates the effect of veratrum in a patient maintained on a low-salt diet.

Case 5.—C. F., a 52-year-old white man, a shoe worker, suffered from headaches and dizzy spells for six months prior to his first visit to the outpatient department. Examination revealed the blood pressure to be 220/120, the heart to be slightly enlarged with no signs of failure, the retinal arteries to be narrowed and sclerotic, and renal function to be unimpaired, with no albuminuria and good concentrating ability.

Treatment with potassium thiocyanate was begun, but despite a blood level of 9 to 11 mg. per cent, maintained for one and one-half months, there was no reduction in the blood pressure and the patient complained of increased dizziness. Potassium thiocyanate was discontinued and

a low-salt diet instituted, salt-free milk powder* and salt-free bread being used. After one month on this regimen the blood pressure fell to 190/110 and the symptoms of headache and dizziness were relieved.

After the blood pressure had been stabilized at 190/110 on repeated clinic visits, veratrum was administered, the diet being continued meanwhile, and the dosage was gradually increased to 30 Craw units every twelve hours. One week after this dosage was attained the blood pressure was 160/100, fluctuating between this value and 175/110 during the next three months. When veratrum was withdrawn the blood pressure rose again to 190/110, promptly falling to 160/100 when the drug was readministered.

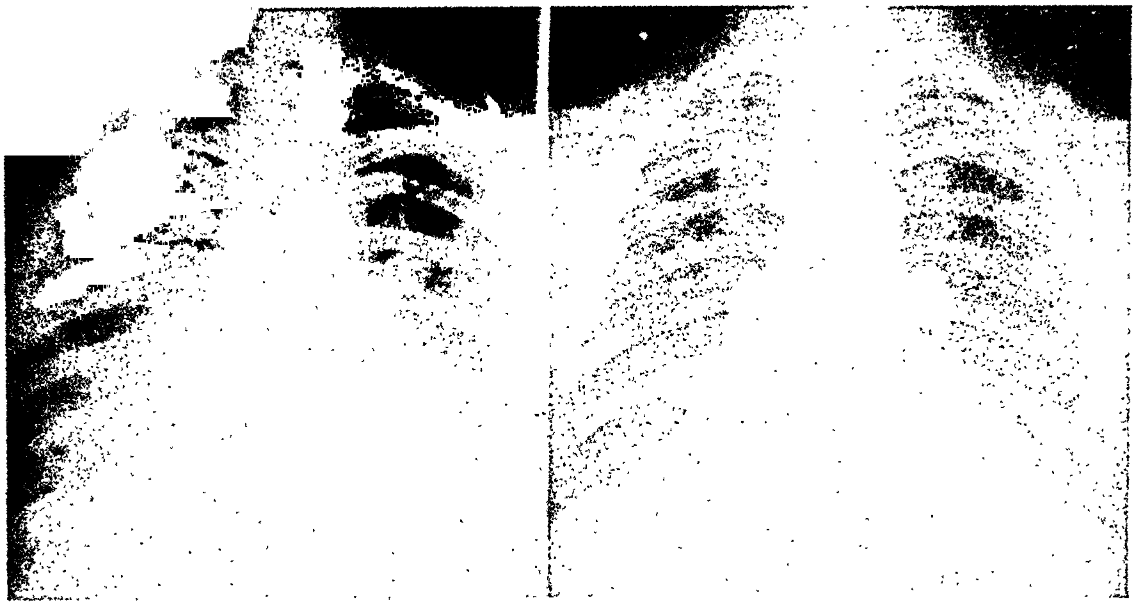

Fig. 5.—The reduction in cardiac size and clearing of pulmonary congestive changes in Patient R. Mc. (Case 4). The roentgenogram on the left was taken prior to treatment and that on the right was taken after seven months of continuous treatment with veratrum viride.

Toxic Reactions and Side Effects.—The reaction to a toxic dose of veratrum viride was in many ways similar to vasovagal collapse.[19] The pulse rate was slowed to between 45 and 60 beats per minute; the blood pressure was markedly reduced, and on one occasion fell to shock levels; there was sweating, nausea, repeated vomiting, salivation, collapse in the erect position, blurring of vision, mental confusion, and a sense of numbness in the extremities and around the mouth.† The bradycardia, but not the hypotension, was relieved by doses of 1.0 mg. of atropine sulfate administered intravenously. The hypotension could be abolished with ephedrine. These toxic reactions, although alarming to the patient, passed off in about five hours, leaving no residua. Such severe effects although largely avoided since the drug has been administered at intervals of eight hours or more, were sufficiently frequent to require careful and frequent observation of all patients under treatment.

Milder side effects occurred, such as nausea, transient blurring of vision, and a sensation of numbness, particularly about the mouth. In some cases, these effects appeared with and in some, before the hypotensive effects, necessitating

*Generously supplied under the name of "Lanolac" by the Mead Johnson Co., Evansville, Ind.

†Such a severe collapse, particularly when associated with a substernal burning sensation, may be mistaken for a coronary occlusion.

the discontinuation of treatment. Occasional attacks of nausea, although not uncommon, were seldom sufficient to cause withdrawal of the medication, but frequently necessitated readjustment of dosage.

The most frequent side effect was a sensation of epigastric burning occurring soon after the ingestion of each dose. This effect was not entirely due to local gastric irritation[1] since similar symptoms were observed following parenteral administration of veratrum viride.

Drug Tolerance.—The phenomenon of tachyphylaxis following the administration of veratrum in animals has been well documented.[5] Tachyphylaxis, apparently, is much less likely to occur with minimal effective doses than with large doses.[4,20] Clinically, in hypertensive patients the development of some degree of drug tolerance was occasionally observed. However, tolerance seldom became complete so that a considerable reduction in blood pressure could still be obtained at the end of twelve or more months of treatment. The typical dramatic result of short-term treatment has been described in Case 1, while the usual less marked hypotensive effect obtained after long-term therapy has been illustrated in Case 3. Occasional patients required less rather than more medication after long-continued treatment.

With continued administration of the drug at a constant dose level it was not unusual to note the sudden or gradual development of nausea and vomiting after days, weeks, or months. Following several such episodes these side effects passed off or in some cases persisted requiring a wider spacing or actual reduction in dosage. The possibility of combatting these developments with the use of tablets containing 5 rather than 10 Craw units, or tablets with enteric coatings, and/or by the use of atropine or hyoscine is under investigation at present.

Adjustment of Dosage.—Since the effective and toxic doses were quite variable in different patients, successful therapy depended upon gradually increasing the dosage in each case and necessitated repeated observations, especially during the early phases of treatment. The following methods of administering the drug were found to be most efficacious. The patient was given an initial dose of 10 Craw units after the morning and evening meals. Outpatients were seen in the clinic after several days of medication, the visit being so arranged that the blood pressure and pulse rate were recorded approximately four to six hours after the patient had received his last medication. Provided that neither a definite hypotensive response nor toxic reactions had occurred, the dosage was increased to 20 Craw units morning and evening administered in subdivided doses of 10 Craw units at hourly intervals, preferably separated by a meal. By such repeated observations of blood pressure, pulse rate, and symptoms, the dosage was increased gradually until a therapeutic effect or toxic reaction occurred.

In hospitalized patients a similar procedure was adapted, or the following more rapid method was used. The rapid method consisted in administering the drug in amounts of 10 Craw units at intervals of two hours while recording the blood pressure and pulse rate responses every half hour until a therapeutic or toxic effect occurred. Minor readjustments of dosage frequently were necessary after the patient had left the hospital.

DISCUSSION

The results of this investigation indicate that veratrum viride is useful in the treatment of certain cases of essential hypertension. The dramatic hypotensive response following short-term administration established the efficacy of the drug in the treatment of so-called "hypertensive crisis." In this condition veratrum was far more effective in our hands than the customary therapeutic methods of venesection or heavy sedation. In addition, the less dramatic but nevertheless significant and prolonged hypotensive effects of veratrum in several severely hypertensive patients, including some with cardiac failure, warrants the hope that such patients may receive lasting benefit from this therapy.

In less severe cases of hypertension, therapy with veratrum was not as useful as in the severe cases. Careful attention to dosage and frequent readjustment of dosage were necessary because of side effects and the development of drug tolerance. Therefore, the milder forms of essential hypertension were more effectively treated by diet, reassurance, sedation, and rest, and, in selected cases, by lumbodorsal splanchnicectomy.

However, cases of long-standing hypertension with marked elevations of blood pressure, not benefitted significantly either by diet or surgery, and more or less incapacitated by the disease, were compensated for the occasional toxic reactions to veratrum by the relief afforded from the symptoms of the disease. In such cases the combined use of a salt-free diet and veratrum viride proved to be more efficacious than either therapeutic agent used alone.

SUMMARY AND CONCLUSIONS

1. Veratrum viride in the form of the whole powdered mixture of alkaloids was administered orally to a series of forty patients with essential hypertension for periods up to thirteen months.

2. When the drug was administered by the oral route, the hypotensive effect began to appear at the end of one or two hours, reached a maximum in four or six hours, and largely disappeared by the end of fourteen hours. In order to obtain maximum therapeutic benefit and to avoid toxic reactions resulting from cumulative overdosage, veratrum was administered at dosage intervals of twelve hours. In addition, in order to provide greater therapeutic safety, this dosage interval was further subdivided so that no more than 10 Craw units were ingested per hour. The great variability of response to a given dose in different individuals required the gradual increase of dosage in each patient in order to avoid toxic side effects.

3. Veratrum was found to be a useful therapeutic agent in the treatment of patients with (a) "hypertensive crisis," (b) severe, long-standing hypertensive disease which proved resistant to other forms of treatment, and (c) hypertension complicated by cardiac failure.

4. Prolonged therapy in some cases resulted in a diminution in cardiac size and reversal of electrocardiographic changes toward normal.

5. There were no deaths and no toxic reactions resulting in more than transient disability attributable to the drug. However, the development of

side effects and of changing sensitivity to a given dose were sufficiently frequent to limit its usefulness in the treatment of patients with mild or moderate degrees of hypertension.

6. Veratrum viride appeared to have therapeutic value as an adjunct to dietotherapy and to the routine treatment of hypertensive heart disease.

The authors wish to thank Dr. Robert W. Wilkins for active cooperation and guidance throughout the period of this study.

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THE EFFECT OF POSTURE UPON AXIS DEVIATION IN HUMAN BUNDLE BRANCH BLOCK

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Our interest in this subject arose from a case of bundle branch block in which serial records showed rather remarkable changes in axis deviation. In Fig. 1, Records *A*, *B*, *C*, *D*, and *E* are consecutive standard limb lead electrocardiograms taken for routine purposes over a period of eighteen months; Records *A*, *C*, and *E* show prolongation of QRS and left axis deviation and were reported as left bundle branch block, whereas Records *B* and *D* show prolonged QRS and right axis deviation and were therefore believed to represent right bundle branch block. We[1] have shown elsewhere that neither right nor left bundle branch block causes great changes in the direction of the mean electrical axis of QRS, so that, even if the side of the block did alternate in this remarkable way, it seems unlikely that this could account for such great changes of axis. In searching for an alternative explanation, we recalled that Ackerman and Katz showed that in experimental bundle branch block in the dog, changes in posture could reverse the direction of QRS in either Lead I or Lead III,[2] and that in human bundle branch block, turning the patient to the left lateral position could reverse the direction of QRS in Lead III, so that discordant left bundle branch was changed to the concordant type.[3] Although the changes in our patient were much more striking, for QRS was reversed in both Lead I and Lead III, it seemed worth while to explore the possibility that even these changes could be due to alterations in the position of the heart. This proved to be the explanation, for with the patient in the supine posture, typical left bundle branch block was present (Fig. 1,*F*) and when the patient turned into the left lateral posture, right axis deviation and apparent right bundle branch block appeared (Fig. 1,*G*).

These observations led us to undertake the present study with the object of discovering how frequently such striking postural changes of axis occur in human bundle branch block. It also seemed advisable to exclude the rather unlikely possibility that the side of the block had actually changed from left to right, for in our patient we had not taken adequate precordial leads in the left lateral posture.

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METHODS

The criteria used for the diagnosis of bundle branch block were those we have previously enumerated.[1] In forty otherwise unselected cases which fulfilled these requirements, twenty patients with right bundle branch block and twenty with left, we have recorded the standard limb leads and Goldberger's augmented unipolar limb leads (aV leads)[4] in the supine, right lateral, and left lateral positions. In addition, in the supine posture, the side of the block was determined from precordial leads recorded by Wilson's technique[5] in the six standard positions,[6] but when left bundle branch block was suspected, a seventh precordial lead was recorded in the posterior axillary line at the level of the fourth, fifth, and sixth standard positions (Lead V_7). In ten of these patients, including all those in whom there could be any suspicion that the side of the block had changed with alteration in posture. the precordial V leads were repeated in the two lateral postures. In all instances gross delay in the appearance of the intrinsic deflection[7] was demonstrated on one side of the precordium only; there is, therefore, no doubt of the side of the block in any of these patients.

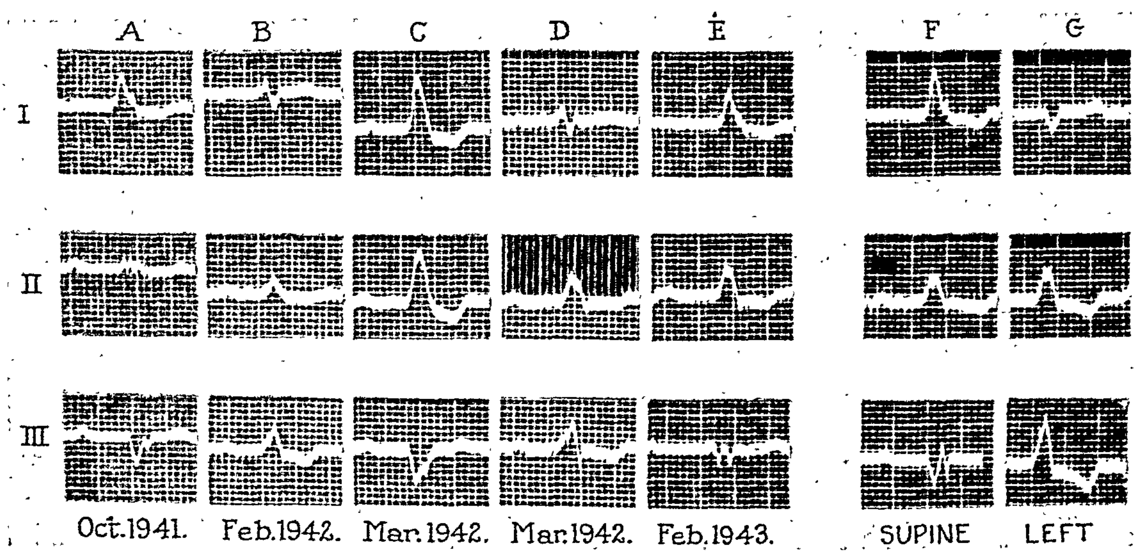

Fig. 1.—*A*, *B*, *C*, *D*, and *E* are standard limb lead electrocardiograms showing apparent alternation of right and left bundle branch block in consecutive records. *F* is an electrocardiogram taken in the supine posture showing left bundle branch block; *G* is taken on the same occasion with the patient in the left lateral posture and shows apparent right bundle branch block. Presumably, these postural changes account for the variations in *A*, *B*, *C*, *D*, and *E*.

Measurement of Axis Position.—By Dieuaide's method,[8] the position of the electrical axis was measured in the standard limb leads with the patient in the supine, right, and left lateral postures. A representative number of complexes was measured, and if the axis position varied with respiration, the extremes were measured and the average recorded. For descriptive purposes we have accepted as the normal axis position the arbitrary limits of 0° to +90° proposed by Carter and associates.[9]

The Electrical Position of the Heart.—From Leads aV_L and aV_F the electrical position of the heart was determined in each posture by the method of Wilson and his collaborators.[10]

RESULTS

Left Bundle Branch Block (Twenty Cases).—

Changes of Axis Position: Changes of axis of 30° or less seemed unlikely to be of much practical importance, and in twelve of twenty cases, alterations of posture did not cause axis changes exceeding that amount. In the remaining eight cases, the axis position shifted more than 30° when the patient moved from the supine into one or other lateral posture; in three cases this occurred when the patient turned into the right lateral posture, in three, with assumption of the left lateral posture, and in two cases, with assumption of either lateral posture (Table I). Six of these shifts of axis exceeded 60°; in one instance (Case L 18) the axis rotated 129° to the right when the patient turned into the left lateral position, and in another patient (Case L 19), assumption of the right lateral posture caused the electrical axis to rotate 185° to the right, while turning from the supine into the left lateral posture caused almost as great a rotation in the same direction (173°). With one exception (Case L 12) all shifts of axis exceeding 30° on the assumption of a lateral posture were to the right.

Changes of Axis Classification: In the supine posture the electrical axis fell within normal limits in seven of twenty cases; in the remaining thirteen cases abnormal left axis deviation was present. In the lateral postures the axis classification remained unchanged in fourteen cases. Of three patients with normal axis position in the supine posture, two (Cases L 2 and L 13) remained within normal limits in the right lateral posture and changed to abnormal right axis deviation in the left lateral posture. In the remaining patient (Case L 12) the normal axis position was unaltered in the left lateral posture but abnormal left axis deviation appeared in the right lateral posture. In three patients with abnormal left axis deviation in the supine posture, two (Cases L 8 and L 18) fell within normal axis limits in the right lateral posture and in the left lateral posture one of these reverted to abnormal left axis deviation (Case L 8) and the other changed to abnormal right axis deviation. In the remaining patient (Case L 19) with abnormal left axis deviation in the supine posture, abnormal right axis deviation was present in both lateral postures.

Changes of Electrical Position of the Heart: In the supine posture the electrical position, determined from the augmented unipolar limb leads, was horizontal in twelve cases, semihorizontal in two cases, intermediate in four cases, and semivertical in two cases. In fourteen cases changes of posture did not alter the electrical position. Of three patients with hearts in the horizontal position in the supine posture, two (Cases L 8 and L 18) assumed an intermediate electrical position in the right lateral posture, and in the left lateral posture one became semihorizontal and the other (Case L 18), vertical; in the remaining patient (Case L 19), the electrical position changed from the horizontal to the vertical when either lateral posture was assumed. Two patients with intermediate

TABLE I. THE EFFECT OF CHANGES IN POSTURE UPON THE ELECTRICAL AXIS, THE ELECTRICAL POSITION OF THE HEART, AND THE ELECTROCARDIOGRAPHIC PATTERN

CASE	AXIS POSITION			AXIS CLASSIFICATION			ELECTRICAL POSITION			EFFECT ON ECG PATTERN	
	S (DEGREES)	RIGHT (DEGREES)	LEFT (DEGREES)	S	RIGHT	LEFT	S	RIGHT	LEFT	TURNING TO RIGHT	TURNING TO LEFT
L 2	+40	+53	+116	N	N	R	Int.	SV	V	—	Reversal QRS_1
L 7	+16	+56	+43	N	N	N	Int.	Int.	Int.	Discordant to concordant	Discordant to concordant
L 8	−12	+24	−25	L	N	L	H	Int.	S. H.	—	—
L 12	+ 8	−33	+20	N	L	N	S. H.	S. H.	S. H.	—	—
L 13	+40	+44	+110	N	N	R	S. H.	S. H.	V	—	Reversal QRS_1
L 18	−10	+30	+119	L	N	R	H	Int.	V	Discordant to concordant	Reversal QRS_1
L 19	−35	+150	+138	L	R	R	H	V	V	Reversal QRS_1	Reversal QRS_1
L 20	+ 6	+ 8	+ 38	N	N	N	Int.	Int.	SV	—	Discordant to concordant

S = supine posture
Right = right lateral posture
Left = left lateral posture
N = normal position of mean electrical axis of QRS (0° to +90°)
L = abnormal left axis deviation
R = abnormal right axis deviation

V = vertical electrical position
SV = semivertical electrical position
Int. = intermediate electrical position
S.H. = semihorizontal electrical position
H = horizontal electrical position

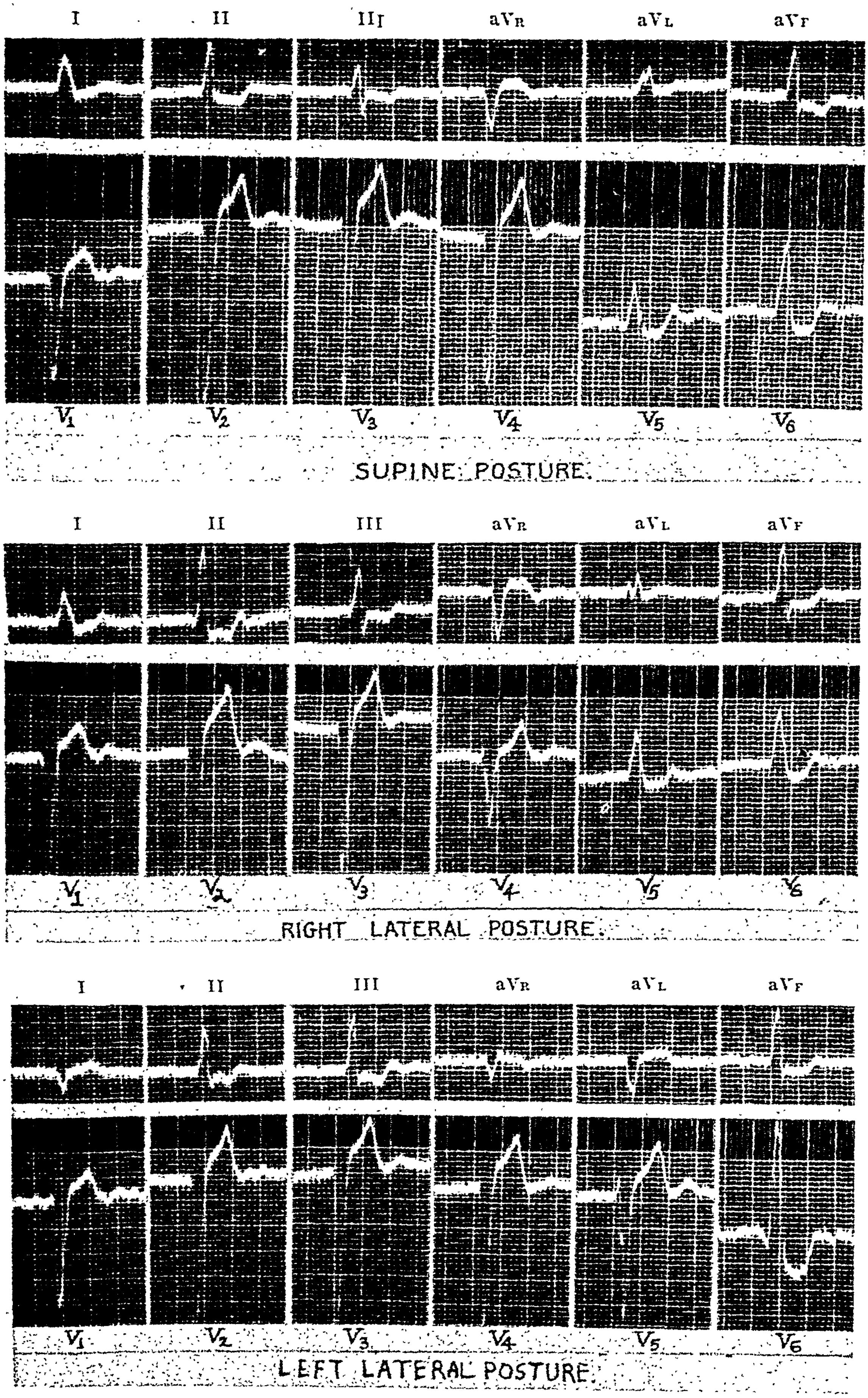

Fig. 2.—Case L 2; left bundle branch block. In the supine posture the pattern is concordant and the position of the heart (aV_L and aV_F), intermediate. In the right lateral posture, the pattern remains concordant. In the left lateral posture, right axis deviation and apparent right bundle branch block appear; the electrical position becomes vertical, but the precordial leads continue to indicate delay of the intrinsic deflection over the left precordium (Lead V_6).

electrical positions in the supine posture assumed semivertical positions in the right lateral posture and vertical positions in the left lateral posture. The remaining patient, with an intermediate electrical position (Case L 20), retained this in the right lateral posture, but assumed a semivertical position in the left lateral posture.

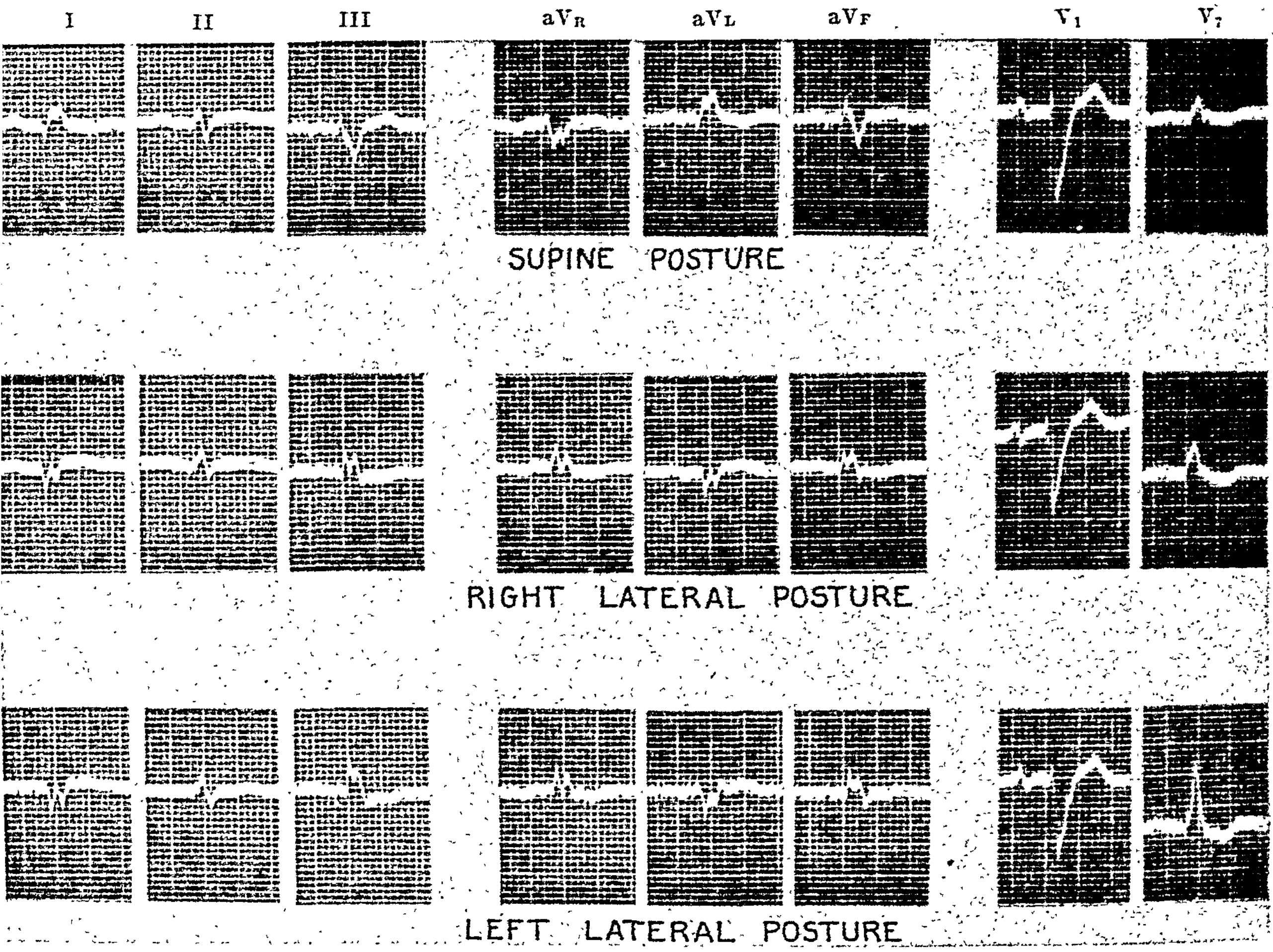

Fig. 3.—Case L 19; left bundle branch block. In the supine posture the pattern is discordant and the electrical position of the heart horizontal. In both lateral positions right axis deviation and apparent right bundle branch block appear, and the electrical position becomes vertical, but precordial leads V_1 and V_7 continue to indicate left bundle branch block.

Effects Upon the Electrocardiographic Pattern: There were striking changes in the general appearance of the electrocardiogram in six cases. In four cases a positive QRS in Lead I became negative, leading to a change from left to right axis deviation, a wide S wave in Lead I, and apparent reversal of the side of the block; in three patients this occurred only on moving into the left lateral posture (Cases L 2, L 13, and L 18) but in one patient (Case L 19) the assumption of either lateral posture was effective. In three cases a negative QRS in Lead III became upright, so that the pattern changed from the discordant to the concordant type of left bundle branch block; this occurred, when the left lateral

posture was assumed (Case L 20), in the right lateral posture (Case L 18), in both lateral postures (Case L 7). The changes in Cases L 2, L 19, L 18, L 20, and L 7 are shown in Figs. 2, 3, 4, 5, and 6, respectively, and all striking changes are summarized in Table I.

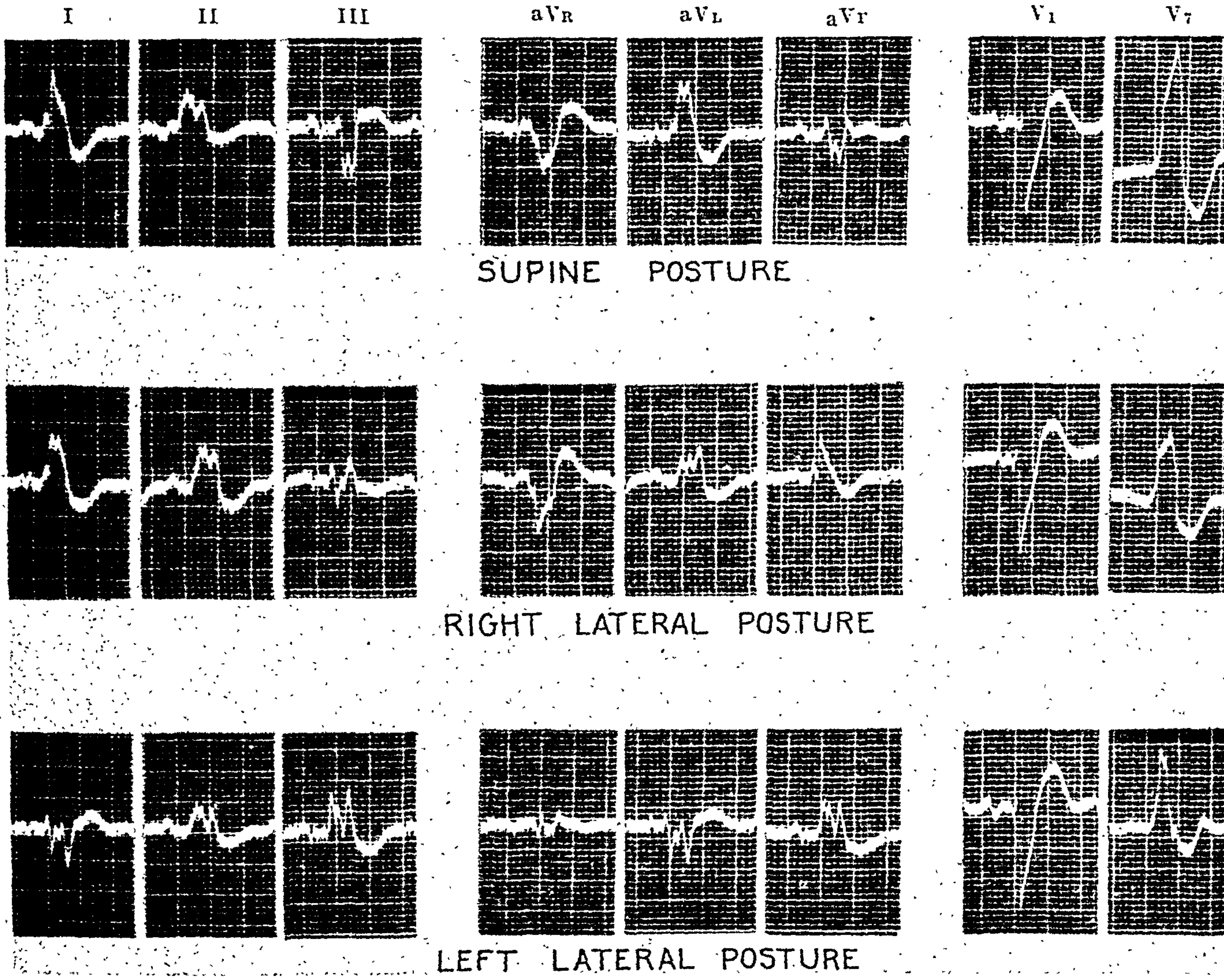

Fig. 4.—Case L 18; left bundle branch block. In the supine posture the pattern is discordant and the electrical position horizontal. In the right lateral posture the pattern is concordant and the electrical position intermediate. In the left lateral posture, right axis deviation and apparent right bundle branch block appear and the electrical position becomes vertical. Chest Leads V_1 and V_7 show left bundle branch block in all postures.

Precordial Leads: All of these changes in the standard and augmented unipolar limb leads occurred without significant changes in the precordial V leads which showed delay of the intrinsic deflection over the left precordium in all postures. In Figs. 2, 3, and 4, right and left precordial leads are illustrated in all postures in the three patients with the most striking limb lead changes (Cases L 2, L 18, and L 19).

Summary: To summarize the postural changes in left bundle branch block: The side of the block, as judged by the standard limb leads, was reversed in one-

fifth (four) of our cases. This reversal was affected most often by assumption of the left lateral posture. The discordant type of left bundle branch block was converted to the concordant type rather less frequently (three cases). Posture did not alter the side of the block when this was decided by precordial leads.

Right Bundle Branch Block (Twenty Cases).—Our observations in right bundle branch block were less striking.

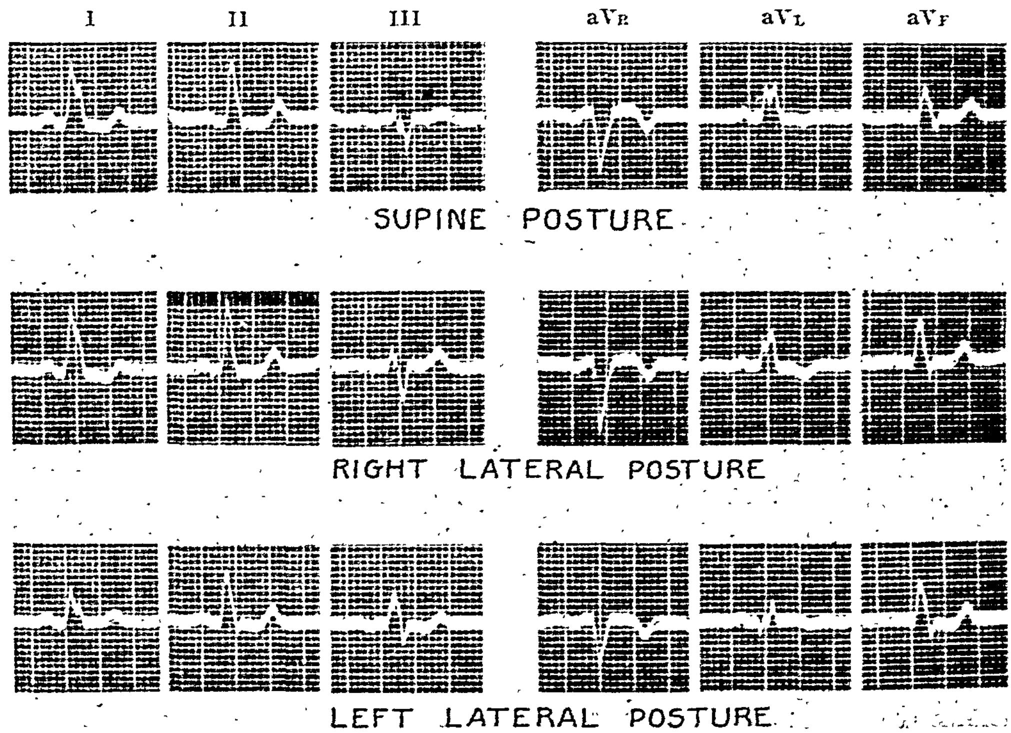

Fig. 5.—Case L 20; left bundle branch block. In the supine posture the pattern is discordant and the electrical position intermediate. There is no material change in the right lateral posture, but in the left lateral posture the pattern becomes concordant because of inversion of QRS in Lead III, and the electrical position becomes semivertical.

Changes of Axis Position: In thirteen patients the postural change of axis was 30° or less; in the remaining seven a change of axis of more than 30° occurred, twice on the assumption of the right lateral posture and five times on turning onto the left side. In only one instance did the axis shift exceed 60° (Case R 16) and in that patient a change in Lead III from a positive QRS of 1.0 mm. to a negative deflection of 1.5 mm. was principally responsible for an axis shift of 110° to the left. This was the sole instance in which assumption of either lateral posture led to leftward rotation of the electrical axis.

Changes of Axis Classification: In the supine posture there were six patients with right bundle branch block with abnormal left axis deviation, nine with normal axis position (0° to +90°), and five with abnormal right axis deviation (more than +90°); changes of posture altered the axis category in only one patient (Case R 16), in whom a normal axis position in the supine posture was converted to abnormal left axis deviation when the left lateral posture was assumed.

Changes of Electrical Position of the Heart: In none of our patients with right bundle branch block was the electrical position changed by alteration of posture.

Effects Upon the Electrocardiographic Pattern: In three patients assumption of the left lateral posture led to standard limb lead records that were difficult to interpret, for the wide S wave in Lead I disappeared. Apart from this, there were no striking changes, and in no instance did the standard limb lead electrocardiogram simulate the appearance of left bundle branch block.

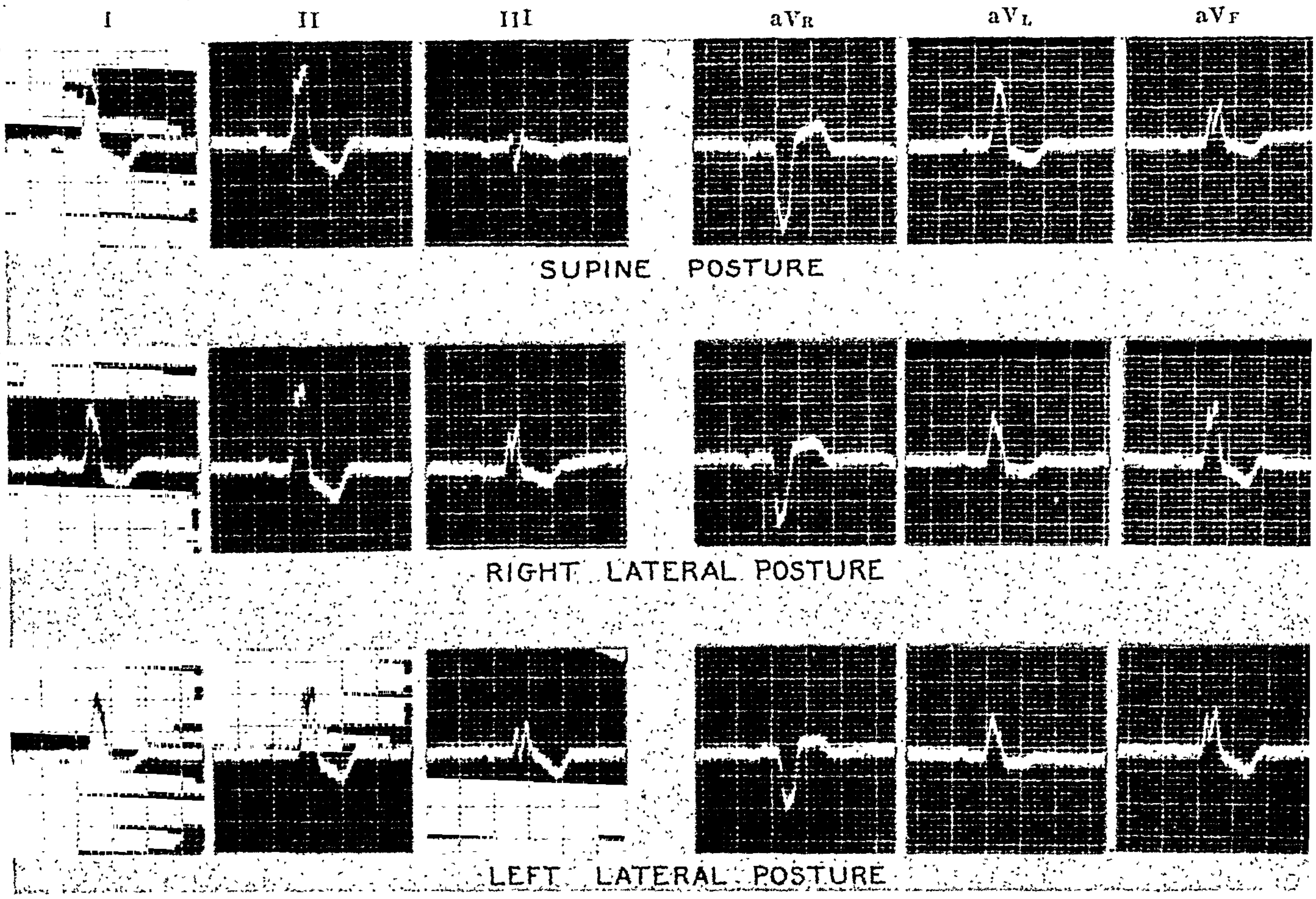

Fig. 6.—Case L 7; left bundle branch block. In the supine posture the pattern tends to be discordant and the electrical position is intermediate (with QRS greater in Lead aV_L than in Lead aV_F). In the right and left lateral postures the pattern is concordant but the position remains intermediate, though QRS is now greater in Lead aV_F than in Lead aV_L.

DISCUSSION

From our observations of these patients we conclude that in left bundle branch block alterations of posture not infrequently cause gross rotation of the electrical axis to the right, the assumption of a vertical electrical position of the heart, and a reversal of the direction of QRS in Lead I so that the standard limb leads come to simulate right bundle branch block. A lesser degree of rightward rotation of the electrical axis leads to conversion of the discordant type of left

bundle branch block to the concordant type. These changes in the standard and unipolar limb leads are not accompanied by any significant change in the characteristic precordial patterns of left bundle branch block.

In 1933, Ackerman and Katz[3] showed that in human left bundle branch block, assumption of the left lateral posture converted the discordant pattern to the concordant in two of six patients, but they were unable to duplicate in human bundle branch block the more striking postural changes they had previously found in experimental canine bundle branch block.[2] They concluded that it was unjustifiable to attempt to locate human bundle branch block from the appearances of the standard limb leads, but this conclusion was strongly criticized by Foster,[11] who pointed out that none of the postural changes produced in man by Ackerman and Katz were sufficiently great to lead to difficulty in deciding the side of the block. Foster claimed also that to produce apparent reversal of the side of the block in the dog required a rotation of axis of 180° and believed this to be most unlikely in man under clinical conditions. Our observations indicate that such changes of axis occur in man not infrequently as a consequence of simple alterations of posture and, probably rarely, even when routine electrocardiograms are made without attempting to alter posture. We, therefore, agree with Ackerman and Katz in their assertion that the standard limb lead electrocardiogram may be unreliable as an indication of the side of the block. Fortunately, since their work, the introduction of multiple unipolar precordial leads has provided a reliable method of localizing the side of the block in the majority of cases, and our observations indicate that the value of this method is not diminished if changes of posture occur. We are, therefore, no longer compelled, as Ackerman and Katz believed, to consider abandoning in man the terminology of right and left bundle branch block.

It seems remarkable that axis shifts as great as 180° (Case L 19) can be produced by the simple expedient of turning onto the side. Certainly there could not be so great a rotation of the heart upon its anteroposterior axis; evidence has now accumulated to indicate that other factors are involved. Lewis,[12] in his study of a patient with a rifle bullet embedded in the heart, was able to compare the movement of the anatomic axis radiographically with the changes of the direction of the electrical axis; he found that when the anatomic axis, as indicated by the bullet, moved 6° to 8°, the shift of the electrical axis was 20°. It is, therefore, unnecessary to assume that the shift of the anatomic axis must correspond in magnitude with the electrical axis shift. An explanation for this discrepancy may be found in the work of Meek and Wilson,[13] who observed that simple rotation of the heart on its anteroposterior axis produced much less striking changes in the electrical axis than rotation of the heart upon its long axis. From the extent of the changes in axis in our patients, it seems probable that the latter type of rotation plays a large part in the effects of posture upon the position of the electrical axis. In addition, it is known that the electrical conductivity of tissues contiguous to the heart affects the distribution of cardiac action potentials.[14,15] It is necessary, therefore, to envisage the possibility that changes in the position of the heart may alter its relationship to tissues of differing conduc-

tivity and, in this way, affect the potential differences recorded at the limb roots and, as a result, the appearances of the unipolar and standard limb leads.

From a practical point of view, we consider that our results indicate once again the importance of a standard posture in recording the electrocardiogram, provide yet another example of the fallacy of attributing significance to the axis deviation as an indication of the side of bundle branch block, and emphasize the reliability of adequate precordial leads in deciding this point.

SUMMARY

1. A case of bundle branch block is described in which the block apparently alternated between the right and left branches. The changes in the electrocardiographic pattern were subsequently duplicated by alteration of the patient's posture.

2. The effect upon the standard and augmented unipolar limb leads and upon the precordial leads of changing from the supine to either right or left lateral postures has been studied in forty cases of bundle branch block, twenty of the right and twenty of the left bundle branch.

3. The position of the electrical axis has been measured in each case in the three postures and the electrical position of the heart determined from the augmented unipolar limb leads.

4. In left bundle branch block the axis shifted more than 30° in eight of nineteen cases; in six instances the shift exceeded 60°. The greatest shift was 185°. The direction of shift was, with one exception, invariably to the right on assumption of a lateral posture. The electrical position of the heart became more vertical in all six patients in whom it was altered.

5. In four patients with left bundle branch block, an upright QRS in Lead I became negative so that right axis deviation and apparent right bundle branch block appeared in the lateral posture. In three patients assumption of a lateral posture caused a negative QRS in Lead III to become upright so that the discordant pattern of left bundle branch block became concordant. In all of these patients the precordial leads showed delay in the intrinsic deflection over the left precordium in all postures.

6. In right bundle branch block, assumption of one or the other lateral posture led to a shift of axis of more than 30° in seven of twenty patients; in six of these, the shift was to the right. In no case did the electrocardiographic pattern simulate left bundle branch block, and the electrical position of the heart was never grossly altered.

7. It is concluded that the limb leads are unreliable as a guide to the side of bundle branch block in some cases, but that the precordial leads are little affected by changes of posture. The importance of taking electrocardiograms in a standard posture is re-emphasized.

It is a pleasure to acknowledge our indebtedness for the technical work to Miss Marjorie Frasier, Mrs. Louise Kirk, and Miss Barbara Schuster of the staff of the Cardiographic Department, Lakeside Hospital.

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DETERMINATION OF THE LEVO- AND DEXTROCARDIOGRAM

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THE fundamental work of Lewis[1] and of Wilson and Herrmann[6] has shown that the electrocardiogram represents the algebraic summation of two distinct components, the levo- and the dextrocardiogram. These left and right components usually appear at the same time, but they can be dissociated when bundle branch block exists. This dissociation is not total, however, because activity always begins in one ventricle before it ends in the other. Moreover, in such a case the invasion of the second ventricle takes place through abnormal pathways. For these reasons, the curves of bundle branch block do not allow an exact determination of the levo- and dextrocardiogram. However, if the bundle branch block is incomplete, the curves can be used for this purpose, since in this case the invasion of the incompletely blocked ventricle follows the usual conduction pathway. Incomplete bundle branch block is often a transient condition, so that normal complexes may also be recorded in the same patient. When these two types of curves are available, the levo- and dextrocardiogram can be calculated in the following manner.

Let us call V_1, V_2, V_3 . . . . the successive values of the cardiac potentials, as they can be measured 0.01, 0.02, 0.03 . . . . second after the beginning of the ventricular electrocardiogram. Each of these potentials is to be considered as the algebraic sum of a right and a left ventricular component which we may call, respectively, D_1, D_2, D_3 . . . . and L_1, L_2, L_3 . . . . In the normal electrocardiogram, when these two components begin simultaneously,

$$V_1 = D_1 + L_1 \quad ; \quad V_2 = D_2 + L_2 \quad ; \quad V_3 = D_3 + L_3 \; . \; . \; . \; . \quad (1)$$

If an incomplete left bundle branch block* develops, the recorded tracing will be different, the successive values of the ventricular potentials becoming V'_1, V'_2, V'_3 . . . .

If the invasion of the left ventricle begins with a delay of 0.01 second, then

$$V'_1 = D_1 \quad ; \quad V'_2 = D_2 + L_1 \quad ; \quad V'_3 = D_3 + L_2 \; . \; . \; . \; . \quad (2)$$

As V_1, V_2, V_3 . . . . and V'_1, V'_2, V'_3 . . . . are known, it can be seen that the equations obtained in (1) and (2) make it possible to calculate all the successive values of the levo- and dextrocardiogram.

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*The case of left bundle branch block has been chosen for consideration because left bundle branch block is more favorable for the purposes of this discussion than right bundle branch block.

METHOD

Correct calculations can be made only if the exact value of the delay in left ventricular activation can be determined from the curve of incomplete bundle branch block. This is do·e by recording the normal then the abnormal electrocardiogram in Leads I, II, III, and CR_5 simultaneously. The time that elapses between the beginning of the earliest QRS wave in any one of the limb leads and the moment at which the intrinsic deflection occurs in Lead CR_5 are measured, first in the normal, then in the abnormal electrocardiogram. The difference between the two values represents the delay in left ventricular activation in the case of incomplete bundle branch block.

This determination can be checked by a different method, provided that the same patient also shows complexes of complete left branch block. The very beginning of the curves of complete and incomplete left bundle branch block is identical in shape and represents a true dextrocardiogram. The moment when these two curves begin to differ indicates the onset of the levocardiogram in the complex of incomplete branch block, and the value of the left ventricular delay is thus known.

The normal and abnormal complexes have been recorded in the same tracing while the patient holds his breath; the incomplete bundle branch block is usually induced by a slight acceleration of the sinus rhythm or by auricular extrasystoles. The complexes of interest to this study have been enlarged by means of a projection lantern and redrawn on a millimetric scale. The successive values of the electrical potentials in the different leads have thus been measured with an accuracy of 0.03 millivolt at intervals of 0.01 or 0.005 second. The value of the left ventricular delay has generally been established with an accuracy of 0.003 second.

RESULTS

Fig. 1 shows the enlarged records of the QRS deflections of a normal and an abnormal beat, both obtained in the same patient. Lead CR_5, not reproduced here, shows that the intrinsic deflection occurs 0.014 second later in the abnormal than in the normal complex. From these data the QRS deflections of the levo- and dextrocardiogram were calculated and the results are shown in the same figure.

Similar determinations have been made in ten patients with transient incomplete left bundle branch block and the results are in general agreement with those of the particular case reported here. When the electrocardiogram does not show any important axis deviation, the levo- and dextrocardiogram are never very different from each other. Their general contour is approximately the same as that of the normal electrocardiogram, except that their voltage is lower,

The most characteristic features are that in Leads I and II the levocardiogram shows Q but no S waves, whereas the dextrocardiogram shows S but no Q waves. It may be concluded, therefore, that in Leads I and II of the normal electrocardiogram, Q and S correspond, respectively, to left and right ventricular activity. This confirms the observation made previously by Sodeman and coworkers[3] concerning the origin of the Q wave of Lead I.

The manifest value of R is higher and the orientation of its axis is slightly more to the left for the levocardiogram than for the dextrocardiogram (Fig. 2). The rotation of the electrical axis generally occurs in a clockwise direction in both levo- and dextrocardiogram. Fig. 1 does not picture the S-T segment or the T wave because they do not show any particularity: the S-T segment is isoelectric and the T waves of Leads I and II are upright in both the levo- and dextrocardiogram.

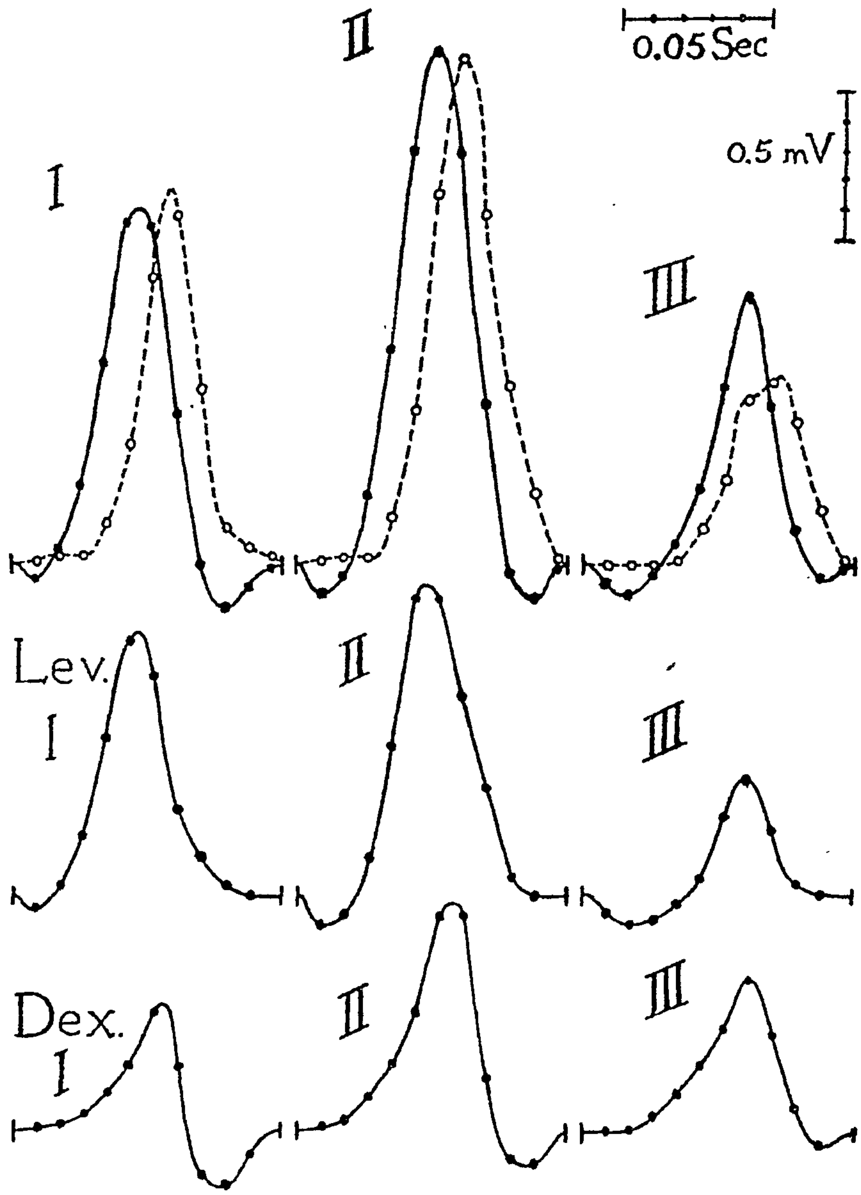

Fig. 1.—*Upper tracings*: QRS deflections of a normal complex (unbroken lines) and of a complex with incomplete left branch block (broken lines), recorded in the three limb leads simultaneously. Vertical lines at the beginning and at the end of QRS indicate synchronous moments in the three leads.
Lower tracings: Calculated QRS deflections of the levo- and dextrocardiogram.

The same patient also shows occasional complexes of complete left bundle branch block. If these are recorded and enlarged by the same procedure and the already calculated dextrocardiogram is subtracted from these complexes, the difference reveals the pathologic levocardiogram of the bundle branch block type (Fig. 3). This figure is completely different from that corresponding to the

normal invasion of the left ventricle. There is a very marked left axis deviation (Fig. 2), the duration of QRS is about 0.10 second, the rotation of the electrical axis is counterclockwise in direction, T_1 is inverted, and the S-T segment is displaced in a direction opposite to the QRS deflection. The onset of this pathologic levocardiogram occurs 0.02 to 0.03 second later than the onset of the normal dextrocardiogram, although the delay in the activation of the left ventricle amounts to 0.05 second. This discrepancy results from the longer duration of the invasion.

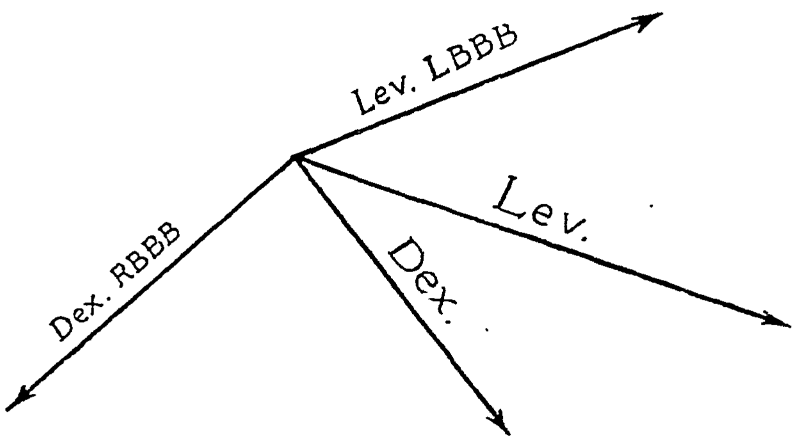

Fig. 2.—Manifest value and axis orientation of the R wave in the normal levo- and dextrocardiogram and in the pathologic levo- and dextrocardiogram of the bundle branch block type.

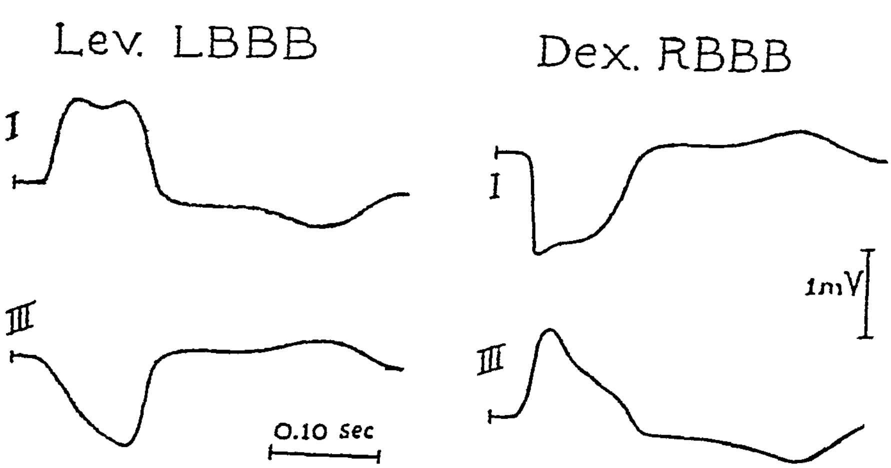

Fig. 3.—Pathologic levo- and dextrocardiogram of the bundle branch block type in Leads I and III. The curves are calculated by subtraction of the normal dextro- and levocardiogram from the recorded left and right bundle branch block electrocardiograms.

In another patient with transient incomplete left bundle branch block whose levo- and dextrocardiogram had been calculated, some complexes of complete right bundle branch block of the uncommon type were also recorded. By subtraction of the levocardiogram from this latter curve, the pathologic dextrocardiogram represented by Fig. 3 was obtained. This curve is definitely abnormal: there is an important right axis deviation (Fig. 2), the duration of QRS

is about 0.10 second, the rotation of the electrical axis takes place in a clockwise direction, and the S-T segment is displaced upward in Lead I.

These levo- and dextrocardiograms of the bundle branch block type correspond to the curves formerly obtained by several authors, but it is obvious that they do not correspond to a normal ventricular invasion.

DISCUSSION

The accuracy of this method of determining the levo- and dextrocardiogram can be proved by the following fact. If the algebraic summation of the right and left components is made with different degrees of delay of the levocardiogram with regard to the dextrocardiogram, the calculated curves reproduce exactly the recorded electrocardiogram of different degrees of incomplete bundle branch block (Fig. 4). This correlation between the calculated and the recorded curves remains very close as long as delay on the left does not exceed 0.02 to 0.03 second.

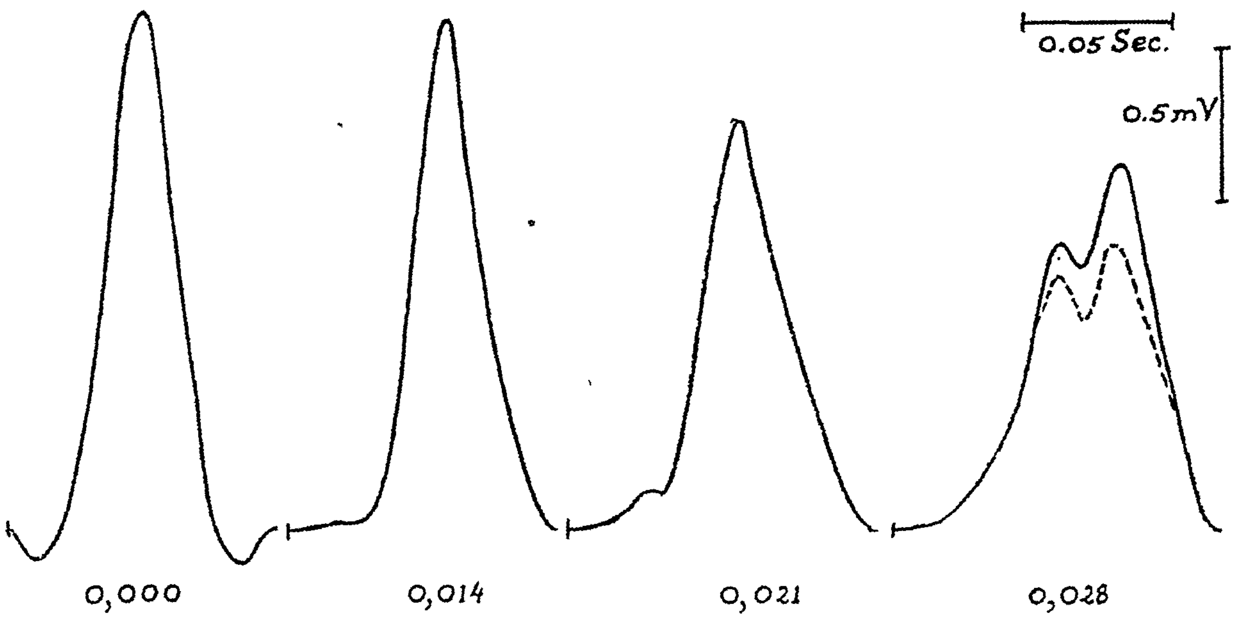

Fig. 4.—Patient showing different degrees of incomplete left bundle branch block. Unbroken line: One normal QRS complex and three QRS complexes with various degrees of left ventricular delay recorded in Lead II. Broken line: Calculated curve for the corresponding degrees of delay of the levocardiogram with regard to the dextrocardiogram. The two lines are perfectly superimposed and therefore indistinguishable as long as the left ventricular delay does not exceed 0.021 second (the left delay is indicated in seconds under each complex).

This method of calculation of the levo- and dextrocardiogram assumes that the invasion pathway is not altered in incomplete bundle branch block. The fact that the recorded curves really satisfy Equations 1 and 2 clearly demonstrates the validity of this assumption. On the other hand, we have previously recorded the vectocardiogram of incomplete left bundle branch block,[2] and the curve does not reveal any notching characteristic of an abnormal pathway of conduction,[4] provided that the delay does not exceed 0.02 to 0.03 second.

These facts indicate that an abnormal pathway of invasion exists when the delay in the bundle branch exceeds 0.02 to 0.03 second. It is, therefore, probable that in this case the left ventricle is simultaneously activated through the normal

and an abnormal pathway, and that the levocardiogram represents a kind of mixed beat. These conclusions are in accord with the fact that in complete left bundle branch block the pathologic levocardiogram begins 0.02 to 0.03 second after the onset of the normal dextrocardiogram.

It has been assumed in Equation 1 that the onset of the levo- and dextrocardiogram is simultaneous in the normal electrocardiogram. This is certainly not always correct, but even if there is normally a slight delay of the levocardiogram, this does not modify the validity of the set of equations: in such a case it would simply be found by the calculations that the value of L_1 is zero. Simultaneous recording of Leads CR_2 and CR_5 in this series of ten cases often revealed the other eventuality, a slight delay of the dextrocardiogram.

The curves obtained here show that the normal levo- and dextrocardiogram must no longer be considered as mirror images with opposite axis orientation. This view arose because the former conception of the levo- and dextrocardiogram was based upon a study either of pathologic bundle branch block or upon the monopolar mode of derivation.[5] Since these curves of bundle branch block are the result of an abnormal mode of invasion or of a particular mode of exploration of the heart, they cannot be used to reconstruct the normal electrocardiogram.

SUMMARY

A method of determining the normal levo- and dextrocardiogram is described.

The levo- and dextrocardiogram are very similar to a normal bicardiogram but of lower amplitude. The main difference between them is that in Leads I and II the levocardiogram shows a QR and the dextrocardiogram, an RS deflection. The manifest value of R is higher and the angle αR somewhat smaller for the levo- than for the dextrocardiogram. The rotation of the electrical axis usually occurs in a clockwise direction for both.

These results do not substantiate earlier concepts concerning the levo- and dextrocardiogram.

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FURTHER EXPERIENCE WITH THROMBOANGIITIS OBLITERANS IN WOMEN

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ALTHOUGH thromboangiitis obliterans in women is still a rare disease,[1-10] recent experience appears to show that it is occurring with increasing frequency. In the first 1,000 patients with this disease seen by the writer, there were only two women,[6] but in the last 600 there have been twenty-three women. Although the incidence for the entire group is only slightly over 1 per cent, in the past ten years it has risen to 4 per cent.

During the past twenty-five years women increasingly have adopted the habit of smoking, and many of them smoke excessively. Since, in my opinion, the use of tobacco by individuals susceptible to this substance is the etiological factor causing thromboangiitis obliterans,[11] it is not difficult to understand why more women are showing signs of this illness. Furthermore, this trend is likely to become more pronounced in the future. Physicians must be alert to the possibility that circulatory disease of this type is present when young female patients complain of discomfort in the extremities.

This presentation is based upon the study of twenty-five female patients with thromboangiitis obliterans seen in private and clinic practice. The essential criterion used in making this diagnosis was the presence of symptoms and signs of obliterative vascular disease in the extremities in women between the ages of 20 and 45 years. A history of intermittent claudication, coldness of the extremities or change of color with different positions of the extremities was usually present in varying degree. The occurrence of superficial phlebitis or painful ulcerations of the fingers or toes with operative or spontaneous loss of digits or amputation of the extremities in persons in this age group gave added weight to the diagnosis of thromboangiitis obliterans. Absence of some major pulsations in the upper or lower extremities was noted in nearly all cases. Evidence of impairment in the circulation was confirmed by oscillometric studies in all cases and by temperature studies in some.

In order to exclude individuals with peripheral vascular disease due to arteriosclerosis, patients with diabetes, gout, or syphilis were not considered in this series. These disorders are known to hasten the development of arteriosclerosis. Hypertension militated against the inclusion of a case when it was clear that an

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elevated blood pressure had existed prior to the appearance of symptoms of arterial obstruction. Individuals in whom calcified vessels could be visualized by x-ray films were excluded. Arteriosclerotic vascular disease without x-ray evidence of calcification is frequently present in patients who first present symptoms of impaired circulation between the ages of 45 and 55 years, and such cases were not included in this series.

CASE HISTORIES*

CASE 1 (1529).—H. B., an American Hebrew woman, 29 years of age when first seen in 1932, was in perfect health until August, 1931. While stepping out of the water at a beach she felt pain in her left leg which was so severe that she was unable to walk for an hour. She then limped home. Following this episode she continued to have intermittent claudication in the left leg after walking three blocks. In December, 1931, she had been treated by a chiropodist for an ingrown toenail. Gangrene of the left great toe, associated with severe pain, developed. This extended and involved the first and second toes and an extensive portion of the dorsal surface of the left foot. Because of severe pain, nerve section to produce anesthesia of the involved area was carried out by another surgeon. Following this, amputation of the first and second toes was done. In the course of time a granulating wound formed and the foot healed completely. This patient had smoked twenty cigarettes a day for a number of years but discontinued smoking with the onset of the present illness. She was married and had two children.

Examination in December, 1933, showed a young woman in good health except for the condition in the lower extremities. The circulation in the upper extremities was normal. The left femoral artery was open. The left popliteal artery was closed. There was no pulsation in the left foot. All normal pulsations were present in the right foot. The left first and second toes were missing and there was a well-healed scar over this portion of the foot. The oscillometer readings were: left calf, 1.5; left ankle, very faint; right ankle, 2.5. The basal metabolic rate was −11 per cent. Blood volume was 63 c.c. per kilogram. The serum cholesterol was 250 mg. per cent and calcium, 12 mg. per cent. Skin tests showed sensitivity to tobacco, ragweed, and timothy. She continued to show improvement and when examined in 1937 was able to walk any distance without trouble. The pulses in her feet remained unchanged, but the oscillometer readings were improved.

This patient was last seen in May, 1946. She stated that she could walk any distance and had no further trouble with her legs. Her left foot had remained healed. All pulses were present in the right foot, none in the left. The oscillometer readings were: right ankle, 3; left ankle, 0.5.

This is a typical example of a female patient with thromboangiitis obliterans who has never resumed smoking and who has had no recurrence of trouble in her legs in a period of observation of fourteen years. Considerable impairment of circulation persists in the left leg, but function is not impaired for ordinary purposes.

CASE 2 (1936).—M. S., an American Hebrew woman, 33 years of age when first seen in November, 1933, had had attacks of superficial phlebitis on the right leg for the past six years. There had been three such attacks and evidence of the last one was still present. Five weeks previously the left great toe had become swollen and painful. Pain was severe at night. For the past five years there had been some discomfort in walking. Her menses were regular, usually lasting two to three days. She was married and had two children. She had been smoking fifteen cigarettes a day for the past seven years. Examination revealed a healthy young woman with the exception of the extremities. The radial vessels were open on both sides. The ulnar pulses could not be felt on either side, and the Allen test was confirmatory of obstruction in these vessels. Both femoral and both popliteal pulses were present. No pulsation was felt in either foot. The right foot showed marked rubor in the dependent position and striking pallor on elevation. There was evidence of recent phlebitis on the inner side of the left ankle. The tip of the right great toe was tender and there was a fissure at this point. The oscillometer readings were: left calf,

*The first two cases in this series have been published previously.[6]

4.5; left ankle, 1.5; right calf, 3; right ankle, 0.75. Skin tests showed sensitivity to tobacco and ragweed.

No data are available on the subsequent history of this patient.

CASE 3 (2651).—J. B., an English-born Hebrew woman, was 29 years of age when first seen in 1936.

She had had discomfort in the left leg for one year, worse on standing and walking, and could walk only one block without stopping. She had been smoking twenty cigarettes a day for the past five or six years. She was married and had one child. The general physical examination was essentially negative. Circulation in the upper extremities was normal. Both femoral and both popliteal arteries were open. All pulses were present in the right foot. There was no pulse in the left foot. There was pallor of both feet on elevation more marked in the left. There was marked rubor of the left lower extremity in the dependent position. The oscillometer readings were: left calf, 2.5; left ankle, 0.25; right calf, 6; right ankle, 3. Blood volume was 70 c.c. per kilogram. Chemical examination of the blood revealed cholesterol of 340 mg. per cent. The Wassermann test was negative. She was advised to stop smoking and was treated with intravenous injections of 5 per cent saline solution twice a week. Her walking gradually improved and she was able to walk six blocks without discomfort. Saline injections were stopped in 1937.

In March, 1940, about three years after the last visit, she was seen again. She reported that during the past one and one-half years she had resumed smoking. Two months prior to this examination she had struck her right great toe against a chair and an ulceration developed which became larger. She had considerable pain in that foot. At that time there was no pulsation in either foot. The oscillometer readings were: left calf, 0.25; left ankle, 0; right calf, 0.25; left ankle, 0. The right foot showed marked rubor. Both feet were cold. There was a shallow ulcer on the inner side of the right first toe, 2.0 cm. in diameter. She was again advised to stop smoking and to resume saline injections. She was treated for several months with considerable improvement. The ulcer healed and pain was relieved. There was still no pulsation in either foot, but the oscillometer readings had improved and were: left calf, 0.5; left ankle, faint; right calf, 1; right ankle, faint. She was seen again in December, 1945. She stated that she had had no further trouble with her legs and could walk any distance without pain. She does not smoke.

This patient is a typical instance of thromboangiitis obliterans in a woman. When first seen she presented only moderate impairment of circulation in the legs, and she improved quickly under treatment. When she resumed the use of tobacco, the disease was rapidly aggravated, and when seen again she had advanced circulatory impairment in both legs. It is now six years since she has stopped smoking. She is in good condition and has had no further trouble with her legs.

CASE 4 (3609).—H. L., an American gentile woman, was 38 years of age when seen in 1938. She gave a history of having been a heavy drinker and smoker for many years. Two years prior to the examination she had had a stroke involving the left side of the body, particularly the face and arm. She recovered from this condition, but there was a persistent sense of numbness in the left hand. For about one and one-half years she had had intermittent claudication in the left leg after walking three blocks. About two weeks before she was first studied she suddenly developed pain in the right leg and when she was seen, the pain was so severe that she was unable to walk at all. She could not sleep without drugs. Wassermann tests had been repeatedly negative. She was married but had no children.

Examination showed a well-nourished woman. The general physical examination was essentially negative. Her blood pressure was 120/70. Circulation in the upper extremities was normal. Both femoral arteries were open. Both popliteal arteries were closed. There was no pulsation in either foot. There was pallor on elevation and rubor in the dependent position of both feet, more marked on the right side. The anterior half of the right foot was very sensitive to pressure. The oscillometer readings were: left calf, 1; left ankle, faint; right calf, 0.5; right ankle, very faint. The further history of this patient is not known.

This is a typical example of thromboangiitis obliterans in a gentile woman, the first of our female patients who showed cerebral involvement.

CASE 5 (3456).—D. W., a Russian Hebrew woman, was 35 years of age when first seen in 1938. She stated that ten months previously while walking home from the beach she had suddenly felt pain in the left calf. She was able to walk only one-half block thereafter without pain in this leg. There was a history of postoperative phlebitis in the left leg seventeen years previously. For eight months she had been taking thyroid capsules and pituitary extract for reduction of weight. She smoked about twenty cigarettes a day. She was married and had two children. Examination showed a markedly obese woman. The blood pressure was 154/94. General physical examination was essentially negative. Circulation in the upper extremities was normal. Both femoral arteries were open, but the pulse in the left femoral artery was small. The right popliteal pulse was present; the left was absent. There was no pulse in the left foot. All pulses were present in the right foot. The oscillometer readings were: left calf, faint; left ankle, 0; right calf, 10; right ankle, 5. She was instructed to stop smoking and to reduce her weight, but no other treatment was recommended.

This patient was next seen in January, 1945. She stated that she had stopped smoking for three years and that during this time had felt very much better. She then had begun to smoke again and for the past two years she had been unable to walk more than one block because of pain in the *right* leg. Re-examination showed an obese woman who was 100 pounds overweight. Circulation in the upper extremities was normal. The left femoral pulse was present; the right was very small. The popliteal pulses could not be felt. The left dorsalis pedis pulse was present. There was no other pulse in the left foot and there was now no pulse in the right foot. The oscillometer readings were: left calf, 1.5; left ankle, 0.5; right calf, 1; right ankle, faint. Her blood pressure had risen to 170/105. X-ray films of the legs showed no calcification of the blood vessels. A blood cholesterol determination was normal. In May, 1946, a report was obtained from her physician who stated that she continued to maintain good health.

This patient developed hypertension subsequent to the appearance of peripheral vascular disease in her legs. There were no signs of arteriosclerosis anywhere in her body. Usually the blood pressure is normal or below normal in thromboangiitis obliterans. However, hypertension in the later stages of the disease has been observed by the writer in several instances.

CASE 6 (3724).—B. G., an American Hebrew woman, was 30 years of age when first seen in 1939. She stated that four weeks previously, while walking on the street on a very cold day, she suddenly developed pain in both lower extremities and her legs became paralyzed. She was taken home by car and had to be carried to her bed. Her feet were cold and white. She continued to have pain for several days. Mild heat was used over the legs. She developed purplish spots on the tip of the right great toe and at two other places on the right foot. These discolored spots became blisters which opened and discharged. In August, 1938, she had had a transient left hemiplegia with a facial paralysis which persisted for some weeks. She entered another hospital where a diagnosis of arteritis of unknown etiology was made. She had been married nine years and had two healthy children. She had been smoking about twenty cigarettes a day for five years. Examination showed a well-nourished, healthy looking young woman. General physical examination was negative except for slight residual weakness of the left side of the body. Her blood pressure was 100/70. Circulation in the upper extremities was normal, except that the left radial pulse was somewhat smaller than the right. The left femoral artery was open; the right was closed. Both popliteal arteries were closed. There was no pulse in either foot. There was a blister at the tip of the right first toe and two small red spots on the dorsal surface of the right foot. The oscillometer readings were: left wrist, 1; right wrist, 1.5; left calf, 0.75; left ankle, 0; right calf, 0.5; right ankle, 0. Blood chemical tests were normal. The Kline test was negative. The basal metabolic rate was −16 per cent. An electrocardiogram was negative. X-ray films of the legs showed no calcification in the blood vessels. She was advised to avoid weight bearing until the foot healed, to stop smoking, and to sleep under a thermoregulated heater.

The last report on this patient by her family physician, in September, 1945, stated that her condition was greatly improved since she had stopped smoking; her walking had improved; both feet were warm. The pulses were still absent. She had received no active therapy.

This is a typical instance of thromboangiitis obliterans in a young Jewish woman which is notable because the first clinical manifestation of the disease was a right cerebral thrombosis.

Case 7 (39-7176).—G. A., an American Hebrew woman, was 26 years of age when first seen at The Mount Sinai Hospital in 1939. She complained of red, tender lumps on both legs of six months duration, but had no other symptoms. She was smoking twenty cigarettes daily. Her general physical examination was entirely negative. All pulsations were present in both upper extremities. All pulsations were present in the left foot. The right posterior tibial pulse was absent. The right anterior tibial and dorsalis pedis pulses were present. The oscillometer readings were: left calf, 3.5; left ankle, 2; right calf, 2; right ankle, 2. There was some swelling of the right ankle and foot and evidence of a superficial phlebitis on the inner side of the right leg. A diagnosis of thromboangiitis obliterans was made and she was advised to stop smoking. No other treatment was recommended. Her condition improved. The inflammation on the right leg cleared up and she was able to walk any distance without pain. However, she began to gain considerable weight and for this reason she resumed smoking in 1941.

When next seen in December, 1944, she reported that for six months she had had pain in the left calf after walking one block. Examination at that time showed the left popliteal artery to be closed and no pulse in the left foot. The right posterior tibial and dorsalis pedis pulses were absent. The right anterior tibial pulse was present. The oscillometer readings were: left calf, 0.25; left ankle, very faint; right calf, 3.5; right ankle, 1.5. At this time she stopped smoking and treatment was begun with intravenous injections of 5 per cent sodium chloride solution three times a week. She showed steady improvement and in June, 1946, she was able to walk one-half mile without pain. The pulsations were unchanged, but the oscillometer readings were: left calf, 1; left ankle, 0.5; right calf, 4; right ankle, 1.5. She then again resumed smoking and developed a small, infected ulcer on the plantar surface of the left foot. She was admitted to The Mount Sinai Hospital in March, 1947. With cessation of smoking, rest, and wet dressings, her condition rapidly improved. In September, 1947, her condition was good. She was again able to walk one-half mile without pain.

The diagnosis was made in this case at a stage when only one foot pulse was absent. If this patient had accepted the advice to avoid smoking permanently, she could have spared herself much later trouble.

Case 8 (5619).—J. M., an unmarried German Jewish refugee woman, was 37 years of age when first seen in April, 1940 in the wards of The Mount Sinai Hospital. Seven years previously she had first begun to have pain in the left foot on walking which was relieved by rest. She also had some tingling in the hands in cold weather. Four years previously she had had a Leriche operation on the left femoral artery, with some relief of pain. She was under marked tension and nervous strain during 1937 and 1938. In 1938, she first began to notice pain in the right leg. At that time a Leriche operation was done on the right side without much benefit. Six weeks previously she had developed pain in the right great toe. She kept her leg constantly dependent and it became swollen. She had been smoking at least fifteen cigarettes daily, and frequently more.

Examination showed a well-developed and well-nourished woman who sat most of the time on the side of the bed with both feet hanging down. She complained of constant severe pain. General physical examination was essentially negative. Blood pressure was 104/60. Both brachial pulsations were present. The right radial pulse was small. The right ulnar artery was closed. A small pulse was present on the back of the right hand. There was no pulse in the left wrist. The right femoral pulse was present; the left was absent. Both popliteal arteries were closed and there was no pulse in either foot. There was marked edema of both legs due to the dependent position of the legs. There was an ulcer of the right first toe. The oscillometer readings were: left arm, 3.5; right arm, 4; left wrist, 0.25; right wrist, 0.5; both calves and both ankles, faint. She stopped smoking and was treated with typhoid vaccine injections and sedatives. The ulcer was dressed with cod liver oil ointment. Her condition gradually improved and she was discharged from the ward in June, 1940. Treatment was continued in the Peripheral Vascular Disease Clinic where she received intravenous injections of hypertonic saline solution three times a week. The ulcer healed completely in August, 1940, and her ability to walk improved. Treatment was discontinued in June, 1941.

Following some emotional disturbance, she resumed smoking in 1942, and in December of that year she developed an ulcer on the right first toe. At this time the oscillometer readings in the left and right calves were zero. She was readmitted to the hospital and again was treated with saline injections for a month. However, the ulcer persisted in spite of various forms of conservative treatment. In December, 1944, she was admitted to the Montefiore Hospital where an amputation of the distal half of the left first toe was done. The toe healed slowly and was completely healed in February, 1946. She is now able to walk two blocks without pain and is doing full-time work. There is still no pulse in either foot and the oscillometer readings are unchanged.

This patient was first seen when the circulation in all four extremities was severely affected by thromboangiitis obliterans, and she was suffering severely with an ulcer of the great toe. This healed under treatment, but in spite of her previous painful experience, she resumed smoking and brought on a recurrence of ulceration.

Case 9 (4897).—H. W., an American Hebrew woman, 20 years of age when first seen in 1941, complained of a swollen and painful foot after an accident. The pain was constant and severe. X-ray films of the foot were negative. On physical examination pulsations of the dorsalis pedis vessels were absent. All other pulses were present in both feet. She smoked from twenty to forty cigarettes daily.

In October, 1944, this patient returned with the history that for one year there had been numbness of the left foot on walking one block and difficulty in dancing because of pain in the left foot. She was married but had no children. Examination showed some atrophy of the left calf. The left popliteal artery was closed and there was no pulse in the left foot. The right popliteal and posterior tibial pulses were present; the right anterior tibial and dorsalis pedis pulses were absent. The oscillometer readings were: left calf, 0.5; left ankle, faint; right calf, 3; right ankle, 1. The left foot was cool and showed typical rubor in the dependent position. The circulation in the upper extremities was normal. She was advised to stop smoking and to have saline injections. She was treated irregularly for two months and showed some improvement in walking. When she was last seen in April, 1945, the same pulses were present but the oscillometer readings were: left calf, 1; left ankle, 0.25; right calf, 4; right ankle, 1.75.

Thrombosis of the popliteal artery occurred in this young woman at the age of 22 years. It is not unusual for thromboangiitis obliterans to start at this early age.

Case 10 (5533).—M. H., a Russian-born Hebrew woman, was 30 years of age when first seen in October, 1942. For two and one-half years she had had pain in the left lower extremity on walking, and for one year she had been able to walk only ten steps without stopping. A painful ulcer had been present on the left third toe for a few months. She had started to smoke at the age of 16 years and had been smoking twenty cigarettes a day since then. She was married and had one child. The general physical examination was essentially negative. Circulation in the upper extremities was normal. Both femoral and both popliteal arteries could not be felt. There was a small right posterior tibial pulse. No other pulse could be felt in either foot. The oscillometer readings were: left calf, faint; left ankle, 0; right calf, 1; right ankle, 0.5. There was a small superficial ulcer about 0.5 cm. in diameter on the outer side of the left third toe. The left foot was much cooler than the right. She was advised to stop smoking and a course of intravenous saline injections was instituted. She showed steady improvement; in December, 1942, the ulcer was almost healed, there was practically no pain, and she was able to sleep without medication. Treatment was continued until May, 1944, at which time she was in excellent condition.

This patient was last seen in June, 1946, and was still in good condition. However, her brother had been killed in the war about a year before, at which time she had resumed smoking. She was warned that she was inviting further trouble.

This patient, like so many others, illustrates the difficulty of weaning individuals permanently from the tobacco habit. Although they admit they realize the danger to their health, any upsetting emotional experience causes them to "reach for a cigarette," and soon they are smoking heavily again.

CASE 11 (5944).—E. B., an American Hebrew woman, was 31 years of age when first seen in 1943. For three years she had had pain in the left calf and foot on walking. She had been smoking twenty cigarettes a day since the age of 14 years. She was married and had three children. The general physical examination was essentially negative. Circulation in the upper extremities was normal. Both posterior tibial pulses were absent. Both anterior tibial and the left dorsalis pedis pulses were present. The right dorsalis pedis pulse was absent. The oscillometer readings were: left ankle, 1.5; right ankle, 3.5. Both feet were fairly warm. She was advised to stop smoking. No other treatment was recommended. In September, 1945, she reported by letter that her condition was much better. However, she has never returned for examination.

CASE 12 (6111).—B. S., an American Hebrew woman, was 33 years of age when first seen in September, 1943. She stated that she had had blueness of the hands for seven years and of the feet for two years. Two and one-half years previously she had had an ulcer of the right index finger which took over one year to heal. This recurred and again took one year to heal. Later she developed gangrene of the left index finger and lesions on her left thumb and fifth finger which also healed slowly. Four months previously she developed an ulcer on the right third finger. This was extremely painful and was not relieved by large doses of sedatives. There was no history of any trouble with walking. She had begun to smoke at the age of 15 years and smoked about a package of cigarettes a day. She had been taking four grains of thyroid extract daily because of overweight and had also received pituitary extract. A body rash had been present for the past seven years. She was married but had no children at the time she was first seen; she had had one miscarriage. However, she had a normal pregnancy and delivery in 1945.

Examination showed a considerably overweight young woman. The general physical examination was negative. The right hand was considerably swollen. The thumb and fifth fingers were normal. The end of the second finger was scarred. There was an ulcer about 1.0 cm. in diameter over the outer side of the right middle finger overlying the distal joint; this was covered with a scab. There was a similar lesion on the inner side of the fourth finger also overlying the joint. The tip of the fourth finger was scarred. The right radial pulse was present; the right ulnar pulse was absent. The left hand was not swollen. The tips of all the fingers were cyanotic. The tip of the left fifth finger was slightly scarred. There was an ulcer 3.0 mm. in diameter on the palmar surface of the terminal phalanx of the left thumb, covered with a scab. The area was extremely tender. The left radial pulse was present; the left ulnar pulse was absent. The toes of both feet were somewhat cyanotic. All pulses were present in both feet, but were small.

The oscillometer readings were: left ankle, 1; right ankle, 1. There was an extensive patch of dermatitis on the back with a sharply defined margin. The skin was reddened and slightly scaly. There was a similar area over the pubis and on the left thigh. The blood Wassermann was negative. An electrocardiogram was normal. X-ray films of the right hand showed no abnormality in the bones or soft tissues. She was advised to stop smoking and to stop the use of thyroid extract and sedatives; typhoid vaccine, intravenously, and cod liver oil ointment for the ulcers were recommended. On this treatment she began to show steady improvement. When she was seen in November of the same year, the pain was entirely relieved and the ulcers on the second and fourth fingers were healed. There was a granulating wound on the middle finger about 1.5 by 2.5 centimeters. She was now advised to have saline injections intravenously in place of the typhoid vaccine, and with this treatment the fingers healed completely. In February, 1944, she returned with a small blisterlike lesion on the tip of the right fourth finger which had been present for about two weeks. The other fingers remained healed. This lesion gradually became larger and she was again treated with typhoid vaccine injections. The finger healed and she was not seen again until September, 1945. At this time she had a painful ulcer on the left third finger. She has not returned for examination since then.

This patient illustrates to a striking degree the tendency of women patients with thromboangiitis obliterans to have serious involvement of the upper extremities before there are symptoms in the feet. In this case, an erroneous diagnosis of Raynaud's disease was accepted by the writer on a first casual examination, but this error was quickly recognized when symptoms persisted. As soon as the true nature of the condition was realized and proper treatment instituted, rapid improvement took place.

CASE 13 (7277).—R. G., an unmarried American Hebrew woman, was 30 years of age when first examined in The Mount Sinai Hospital in May, 1943. At that time she complained that for one year she had had attacks of pain in both feet. She was smoking ten cigarettes a day. Her general physical examination was negative. Circulation in the upper extremities was normal. The right anterior tibial and posterior tibial pulses were normal. The right dorsalis pedis pulse was absent. The left anterior tibial pulse was normal. The left posterior tibial and dorsalis pedis pulses were absent. The left foot was slightly cooler than the right. There was slight blanching of the left foot on elevation and both feet were somewhat redder than normal in the dependent position. The oscillometer readings were: left calf, 6; left ankle, 2; right calf, 7; right ankle, 3. A diagnosis of incipient thromboangiitis was made, and she was advised to stop smoking. No other treatment was recommended. However, she continued to smoke.

She was seen again in February, 1945, when she complained of pain in the left calf after walking two blocks and of pain in the toes which interfered with sleep. Examination showed marked progression of the vascular disease in the legs. Both femoral pulses were present. The right popliteal pulse was present; the left was absent. The right posterior tibial pulse was present. There was no other pulse in either foot. The oscillometer readings were: left calf, 0.5; left ankle, 0; right calf, 4.5; right ankle, 2. She had an ulcer on the plantar surface of the left foot. At this time treatment with intravenous injections of 5 per cent saline solution was started. By June, 1945, the ulcer had healed and she was able to walk three blocks without stopping. She complained of dizziness and headaches following the injections of saline and these were, therefore, discontinued.

On her last examination in June, 1947, she was able to walk four blocks without stopping. The right posterior tibial pulse was present. In addition, there was a right peroneal pulse. The right anterior tibial and dorsalis pedis pulses were still absent. There were no pulses in the left foot. The oscillometer readings were: left calf, 1; left ankle, 0.25; right calf, 4.5; right ankle, 2.25.

This patient, like the patient in Case 7, was seen at a time when her circulatory disease was incipient. She refused to follow advice against tobacco and returned with serious impairment of circulation.

CASE 14 (7641).—S. S., an American Hebrew woman, was 29 years of age when first seen at The Mount Sinai Hospital in 1943. Her only complaint was of coldness and pain in the right third finger. She stated that she had first begun to smoke *at the age of 9 years*, and that in recent years she had been in the habit of smoking twenty cigarettes a day. She was married and had one child. The involved finger remained persistently cold even when the feet were kept in hot water for forty-five minutes. All pulsations were present at both wrists and in both feet. A diagnosis of incipient thromboangiitis obliterans involving only the digital vessels of the right third finger was made. Cessation of smoking was advised but no other treatment was recommended. She stopped smoking for about one year and her symptoms disappeared, but she resumed smoking because she was gaining weight.

She was seen again in June, 1945, when she complained of pain in her right leg after walking one and one-half blocks. The general physical examination was negative. The left ulnar pulse was absent. All the other pulses were felt in both upper extremities. All pulsations were present in the left lower extremity. The right femoral pulse was present. The right popliteal pulse was absent and there was no pulse in the right foot. The oscillometer readings were: left calf, 5; left ankle, 3; right calf, 1; right ankle, faint. There was hypesthesia of the right foot and blanching on elevation. She was again advised to stop smoking and treatment with saline injections was instituted. Her condition thereafter showed steady improvement. On last examination, in January, 1947, she stated that she was able to walk four blocks without pain. All pulses were present in the left foot, and a small dorsalis pedis pulse could be felt in the right foot. The oscillometer readings were: left ankle, 2.5; right ankle, 0.5.

This case is interesting because of the onset of thromboangiitis obliterans in the right upper extremity at a time when there were no symptoms or signs of vascular disease in the legs.

CASE 15 (44-1157).—T. P., a Hebrew woman, was 24 years of age when first seen at The Mount Sinai Hospital in March, 1944. For one and one-half years she had had pain in the left

calf after walking five blocks or after dancing. She had been smoking twenty cigarettes a day. She was married but had no children. Examination showed a well-nourished young woman whose general physical examination was negative. The right radial and left ulnar pulses were absent. The right ulnar and left radial pulses were present. Both femoral pulses were present. The right popliteal and right posterior tibial pulses were present. The right anterior tibial and dorsalis pedis pulses were absent. The left popliteal artery was closed and there was no pulse in the left foot. The oscillometer readings were: left calf, 0.5; left ankle, 0.25; right calf, 4; right ankle, 1.5. Blood pressure was 120/70. Blood Wassermann test was negative. It was difficult to persuade this patient to stop smoking, but she finally gave up using tobacco and was treated with intravenous injections of hypertonic salt solution. She showed steady improvement. In June, 1947, she was able to walk indefinitely without pain and without stopping. The pulses in her feet and the oscillometer readings remained unchanged.

This young woman, like the woman in Case 8, had thromboangiitis obliterans involving all our extremities.

CASE 16 (7322).—A. E., an Austrian-born Hebrew woman, was 41 years of age when first seen in February, 1945. In 1942, she began to have burning pain in the right first toe, and in 1944, developed an ulcer on this toe. This ulcer healed after three months of treatment with bed rest, injections of typhoid vaccine, Papaverine, Depropanex, and the use of regulated heat. Recently, the ulcer recurred and ulceration of the fourth toe of the same foot also developed. She had had intermittent claudication for one year. She had smoked twenty cigarettes a day for fourteen years. She was married but had no children.

On examination the left radial pulse was present; the ulnar pulse was absent. The Allen test was positive in the left hand. The right radial pulse was very small; the ulnar pulse was absent. There was a pulse on the dorsal surface of both wrists on the ulnar side. Both femoral arteries were open. The left popliteal pulse was present; the right was absent. The left anterior tibial pulse was present. There was no other pulse in either foot. The oscillometer readings were: left calf, 4; left ankle, 1.25; right calf, 0.25; right ankle, faint. There was tenderness of the right first and fourth toes with evidence of recent infection. There was marked rubor of the right foot and it was cooler than the left. She was advised to stop smoking, to avoid weight bearing, and to have saline injections. When she was last heard from in June, 1946, her ulcers were healed and she could walk five blocks without pain. She stated that she had given up smoking.

CASE 17 (7435).—I. Y., an American Hebrew woman, was 29 years of age when first examined in 1945. Eight years previously she had had a superficial phlebitis of the left leg, and intermittent claudication had developed shortly afterward. In 1942, she had developed gangrene on the inner side of the right great toe. In 1943, she had had a right hemiplegia with aphasia. Ever since then she has had occasional short epileptic attacks involving the right side and characterized by clonic contractions lasting a few seconds; she has also had crying spells. She had begun to smoke when very young and smoked twenty cigarettes a day. She had stopped smoking in 1943. She was married but had no children.

Examination showed a well-nourished young woman. There was weakness of the right side of the face and a hemiparesis of the right side of the body. She had almost complete motor aphasia but could speak a few words. There appeared to be no sensory aphasia. Her blood pressure was 130/80. Both radial arteries were open, but the ulnar arteries were closed. Both femoral arteries were open. Both popliteal arteries were closed. There was no pulse in either foot. There was a scar on the inner side of the right great toe. The oscillometer readings were: left calf, 1; left ankle, faint; right calf, 0.25; right ankle, 0. When she was last examined in June, 1947, her condition was unchanged.

This young woman with typical thromboangiitis obliterans of all four extremities presented the extremely unusual complication of a right hemiplegia and motor aphasia, which had developed at the age of 27 years. Two other women in this series (Cases 4 and 6) showed cerebral involvement.

CASE 18 (7483).—F. Z., an American Hebrew woman, was 42 years of age when examined in April, 1945. She had complained of pain in the left lower extremity on walking for fifteen years.

She was able to walk only one block, slowly. She also had a little trouble in the right leg. Six months previously she had had a lesion on the left index finger and a swelling on the inside of the wrist. She had begun to smoke at the age of 16 years and smoked from twenty to thirty cigarettes a day. She had stopped smoking three months previously and since then the condition of her hands had improved. She was married and had two children.

The general physical examination was essentially negative. All normal pulses were absent in the right wrist, but two abnormal pulses were present on the back of this wrist. The left radial pulse was present; the ulnar pulse was absent. There was moderate rubor of the toes of both feet. Both feet were warm. All pulsations were present in the right lower extremity. The left external iliac pulse was small. The left femoral pulse was absent, and there was no pulse in the left lower extremity. The oscillometer readings were: left calf, 0.5; left ankle, 0.25; right calf, 5; right ankle, 1.5. She was advised to refrain from smoking, to exercise, and to receive intravenous injections of saline solution. She reported by letter in September, 1945, that she was feeling better.

Case 19 (8053).—A. S., an American gentile woman, was 31 years of age when seen in December, 1945, four months after a mid-thigh amputation of the right lower extremity. She stated that she had started to smoke at the age of 19 years and usually smoked twenty cigarettes a day. Two years later, at the age of 21, she first noticed intermittent claudication, chiefly in the right leg, after walking ten blocks. This condition gradually became worse and she was able to walk only two blocks without stopping. In April, 1941, she had a frostbite. She was admitted to the Greenwich Hospital in Connecticut where a diagnosis of thromboangiitis obliterans was made. She was advised to stop smoking, which she did for two and one-half years, but then she started to smoke again. She noticed immediately that her walking became worse. In November, 1943, she developed tenderness near the nail of the right first toe. She returned to the hospital and an incision was made around the nail, resulting in a deep, tender ulcer with exposure of bone. This continued for nine months. She continued to smoke while in the hospital but stopped smoking in 1944. In December, 1944, the great toe of the right foot became inflamed. She was again treated at the Greenwich Hospital with Depropanex and saline injections, intravenously. In August, 1945, gangrene of the right foot developed and a right mid-thigh amputation was then done.

When she was examined in December, 1945, the general physical examination was essentially negative. She had advanced impairment of circulation in the remaining left lower extremity. There was a well-healed mid-thigh stump. The right radial pulse was absent; the ulnar pulse was present. The left radial pulse was present, but the left ulnar pulse could not be felt. The left popliteal pulse was absent and there was no pulse in the foot. The oscillometer readings were: both wrists, 2.5; left calf, faint; left ankle, very faint. She was last seen in September, 1946. She was wearing an artificial leg and was able to walk one block without stopping. She was receiving injections of 5 per cent sodium chloride solution three times a week.

This is the only woman patient with thromboangiitis obliterans seen by the writer who has had an amputation of a leg.

Case 20 (8149).—S. R., an American Hebrew woman, 30 years of age, was first seen in January, 1946. In June, 1944, she had had an attack of pain and swelling of the right ankle. In May, 1945, she began to have intermittent claudication in the right leg after walking two blocks. She was studied at The Mount Sinai Hospital at that time. She was married and had one child. She had begun to smoke at the age of 18 years and smoked twenty cigarettes a day. The general examination, including the Kahn test, urinalysis, and blood count, was negative. The basal metabolic rate was -11 per cent. X-ray films of the right foot were negative. There was persistent absence of the right posterior tibial pulse and some reduction in oscillometer readings. Skin tests to tobacco were positive. A diagnosis of thromboangiitis obliterans was made. She was advised to stop smoking but did not do so. About December, 1945, the right third toe became discolored and painful and three weeks later a black spot developed. On examination at this time, the left foot was considerably cooler than the right. Both femoral and both popliteal pulsations were present. The left anterior tibial pulse was present, but there was no other pulse

in either foot. There was an area of gangrene, 1.0 cm. in diameter, on the mesial surface of the tip of the right third toe. The oscillometer readings were: left calf, 5; left ankle, 1.5; right calf, 4; right ankle, 1. Circulation in the upper extremities was normal. She was again advised to stop smoking and received intravenous typhoid injections for relief of pain. Her condition slowly improved, and when she was seen in June, 1946, pain was much less. The same pulses were present, but the oscillometer readings were: left ankle, 2.25; right ankle, 1.5. The gangrenous area on the right third toe had separated and a clean, healing ulcer was present at the tip of the toe. In October, 1946, the ulcer was completely healed and there was no longer any pain.

Although this patient, like several others in this series, had the benefit of an early diagnosis of thromboangiitis obliterans, she failed to heed advice to give up smoking until she developed gangrene of a toe.

CASE 21 (8304).—S. D., an American Hebrew woman 37 years of age, was first seen in March, 1946. For two years she had noticed numbness of the toes of both feet after walking six blocks. Occasionally, she had swelling of the instep. She smoked fifteen cigarettes a day. She was married and had three children. Examination showed a healthy, well-nourished woman. The general physical examination was negative. Circulation in the upper extremities was normal. Both feet were cold. Both femoral and both popliteal pulses were present. There was no pulse in either foot. The oscillometer readings were: left calf, 5; left ankle, 1.5; right calf, 5; right ankle, 1. There was rubor of both feet on dependency and blanching on elevation. She was advised to stop smoking and was encouraged to walk several miles daily. No other treatment was recommended.

This is a typical early case of thromboangiitis obliterans in a woman. If she obeys instructions to avoid tobacco it is unlikely that she will have further trouble with her legs.

CASE 22 (8471).—L. A., an American Hebrew woman 24 years of age, was seen in May, 1946. She gave a history of having had an injury to the right third finger in Septenber, 1943. X-ray films were negative for fracture. The finger continued to be painful and an ulcer developed on the tip; the finger also became gangrenous. There was no improvement after conservative treatment for four months. She was then hospitalized and the terminal digit of the right middle finger was amputated. Some months after this she began to have pain in the left index finger. After an injury to this finger, gangrene developed at the tip and a small part of the finger sloughed away. Since then, the left fifth and the right fourth and fifth fingers had become painful and had developed secretion under the nails. Later, the left fourth finger became similarly affected. Recently, she developed a small ulcer on the left first toe. The patient had begun to smoke at the age of 16 years and smoked about twenty cigarettes daily. Although she was advised to stop, she has never done so for more than a week. The general physical examination showed a well-nourished young woman and was essentially negative. The left thumb was normal. The nail of the left index finger was long and curved and slightly tender to pressure; there was no obvious ulceration or infection. There was a portion of protruding bone at the tip of the left third finger with a surrounding hard crust. The distal joint was ankylosed. There was some swelling of the terminal portion of the left fourth finger with infection beneath the nail. There was a heavy crust at the tip of the left fifth finger. The left second, third, and fifth fingers tapered toward the ends. The distal phalanx of the right third finger was missing; the finger was perfectly healed; there was good motion at the proximal interphalangeal joint. The right thumb was normal. There appeared to be some infection beneath the nails of the fourth and fifth fingers. The tip of the fourth finger was moderately tender. Part of the nail was missing from the right index finger. She was unable to make a complete fist with either hand. All the fingers of the right hand except the thumb were cooler than the fingers of the left hand. Both radial arteries were open; both ulnar arteries were closed. There was a positive Allen test on both sides. The oscillometer readings were: left wrist, 2; right wrist, 2. All pulses were present in the right foot. The left posterior tibial pulse was good. The left anterior tibial and dorsalis pedis pulses were absent. The oscillometer readings were: left ankle, 3; right ankle, 3.5. There was an ulcer mesial to the nail of the left first toe which appeared to be due to the pressure of the sharp edge of the nail. X-ray films of the hand made on three different occasions showed no abnormalities in the tufts of the bones of the terminal phalanges.

A diagnosis of Raynaud's disease had been made by several physicians. However, there were none of the characteristic manifestations to justify this diagnosis. She gave no history of any blanching or other color changes on exposure to cold; she frequently went about without gloves in the winter. Even now, in spite of the ulcers present on many fingers, she still had no complaints of color changes in the fingers on exposure to cold.

CASE 23 (8608).—H. K., an American Hebrew woman 40 years of age, was first seen in June, 1946. For eight months she had had pain in both feet after walking two blocks, worse on the left side. There was no pain at rest. She had been smoking twenty cigarettes a day for two and one-half years. The history was otherwise negative. She was married and had one child. Physical examination showed a well-nourished woman who looked much younger than her age. The examination was essentially negative except for the extremities. Both radial arteries were open. Both ulnar arteries were closed, and the Allen test was positive in both hands. Both femoral and both popliteal pulses were present. All normal pulses were absent in both lower extremities, but there were good peroneal pulses in both feet. The oscillometer readings were: left calf, 5; left ankle, 0.5; right calf, 5; right ankle, 2.5. She was advised to stop smoking and was encouraged to walk several miles each day.

When last seen, in September, 1946, she stated that her feet felt somewhat warmer and that she was able to walk three or four blocks without stopping. However, her circulation remained unchanged and treatment with intravenous injections of 5 per cent saline solution was recommended.

A diagnosis of thromboangiitis obliterans could be made in this patient because of the evidence of impaired circulation in all four extremities, her generally youthful appearance, and the absence of any signs of arteriosclerosis. The late appearance of the disease is explained by the fact that she had started smoking at the age of 37 years.

CASE 24 (8746).—J. A., an American gentile woman 39 years of age, was seen in October, 1946. For two and one-half years she had had attacks of pallor and pain in the left fifth finger. Three weeks previously the left fourth and fifth fingers had turned dark. She had been admitted to a hospital and treated with Dicumarol, niacin, phenobarbital, and intermittent venous occlusion. She was smoking fifty cigarettes daily. There was no complaint of trouble with walking. Physical examination was essentially negative. Circulation in the right hand was normal. The left radial artery was open; the ulnar artery was closed. The Allen test was positive. The left fifth finger was somewhat cooler than the others; it had a glossy, red appearance. The skin of the terminal phalanx was thickened. The finger was tender to firm pressure. All pulsations were present in both feet and were normal in size. The oscillometer readings were: left ankle, 4; right ankle, 3.5. There was some rubor of the toes of both feet. The feet were warm. A diagnosis of thromboangiitis obliterans was made. She was advised to stop smoking, but no other treatment was felt to be necessary.

This is a typical early case of thromboangiitis obliterans with involvement of one upper extremity before any symptoms appeared in the feet.

CASE 25 (8834).—S. P., an American Hebrew women, 31 years of age, was first seen in November, 1946. She gave a history of cramps in the left foot on walking three blocks. The cramps had been present for a year. She had no other complaints. She had begun to smoke at the age of 16 and smoked twenty cigarettes daily. She was married but had no children. Examination showed an overweight young woman whose general physical examination was negative. Both ulnar pulses were absent. Both radial pulses were present. There was marked rubor of the left foot. There was some thickening of the veins on the dorsal surface of the outer side of the left foot. The left femoral pulse was present; the popliteal pulse was absent. There was no pulse in the left foot. All normal pulses were present in the right foot except the dorsalis pedis. The oscillometer readings were: left calf, 0.75; left ankle, faint; right calf, 6; right ankle, 2.5.

This is a typical case of thromboangiitis obliterans in a woman showing involvement of both upper and both lower extremities.

REVIEW OF CASE HISTORIES

Study of the case histories reveals certain facts which require emphasis. The most important finding is that thromboangiitis obliterans in women very frequently involves the hands, and occasionally *begins* in the fingers (Cases 12, 14, 22, and 24) rather than in the feet. In men it is extremely rare for this disease to begin in the upper extremities. In Table I it will be noted that fourteen of the twenty-five cases of women (56 per cent) showed signs of circulatory disease in the upper extremities.

TABLE I. CLINICAL DATA ON TWENTY-FIVE WOMEN WITH THROMBOANGIITIS OBLITERANS

CASE NO.	AGE AT ONSET (YEARS)	NO. OF CIGARETTES SMOKED DAILY	SEVERITY OF INVOLVEMENT*	UPPER EXTREMITY INVOLVEMENT
1	28	20	3 +	No
2	27	15	2 +	Yes
3	28	20	3 +	No
4	36	40	3 +	No
5	34	20	3 +	No
6	30	20	4 +	Yes
7	26	20	3 +	No
8	30	15	4 +	Yes
9	22	40	3 +	No
10	27	20	4 +	No
11	28	20	1 +	No
12	26	20	1 +	Yes
13	29	10	3 +	No
14	29	20	3 +	Yes
15	22	20	3 +	Yes
16	38	20	3 +	Yes
17	21	20	3 +	Yes
18	27	30	4 +	Yes
19	21	20	3 +	Yes
20	28	20	2 +	No
21	35	15	2 +	No
22	21	20	1 +	Yes
23	39	20	2 +	Yes
24	36	50	1 +	Yes
25	30	20	3 +	Yes

*Explanation of degree of circulatory impairment: 4 +: femoral, popliteal, anterior tibial, and posterior tibial arteries closed; 3 +: femoral artery open, popliteal, anterior tibial, and posterior tibial arteries closed; 2 +: femoral and popliteal arteries open, anterior tibial and posterior tibial arteries closed; 1 +: femoral and popliteal arteries and one foot pulse open, one foot pulse closed.

When circulatory disease occurs in the hands of a woman, the differential diagnosis between thromboangiitis obliterans and Raynaud's disease becomes very important. Unless the proper diagnosis is made, treatment is almost certain to be incorrect and unsuccessful. Raynaud's disease is pre-eminently a condition which occurs in women, and involvement of the hands is characteristic. Patients with Raynaud's disease complain of blanching of the fingers on exposure to cold. This is due to spasm of the digital arteries shutting off circulation to the finger tips. Female patients with thromboangiitis obliterans also complain of blanching of the fingers on exposure to cold. This is due to vasoconstriction superim-

posed upon organic disease in the digital vessels. The blanching in Raynaud's disease is likely to involve several fingers, and symmetrical fingers of both hands. The blanching in thromboangiitis obliterans is more likely to involve only one finger of one hand. Pain is not a prominent feature of Raynaud's disease. Patients with this condition complain of tingling during the hyperemic or red phase of the attacks, but between attacks there is usually no pain unless ulceration is present. In contrast, the patient with thromboangiitis obliterans complains of constant pain in the affected finger. This is an important clue to the nature of the illness. On examination, the patient with Raynaud's disease will show equal temperature of all fingers between attacks since it is only during the period of spasm that circulation is temporarily impaired. On the contrary, the patient with thromboangiitis obliterans will show persistent coldness of the involved finger at all times. Finally, examination of the lower extremities will reveal normal arterial circulation in Raynaud's disease, but some pulsations are likely to be absent in patients with thromboangiitis obliterans. If these points are kept in mind it is usually possible to distinguish between the two conditions.

Three of the twenty-five patients (Cases 4, 6, and 17) in this series showed cerebral involvement (12 per cent). The incidence of cerebral involvement in male patients with thromboangiitis obliterans has been less than 1 per cent, and at first glance the higher incidence in women is striking. However, because of the relatively small number of female patients with this disease, this figure cannot be considered significant unless it is confirmed in a much larger series of cases.

It is discouraging to note that women are even more prone to resume smoking and cause recurrence of their trouble than are men. Emotional disturbances, the tendency to put on weight, or recurrence of habit are given as the usual reasons. In such instances, when the patient returns, it is usually found that the circulation is much worse than when she was first seen, and the long course of treatment necessary to improve it must be resumed.

The opportunity to study many additional cases of thromboangiitis obliterans in women has thrown no further light upon the relative immunity of this sex to the disease. The women who developed thromboangiitis obliterans showed no changes in menstruation, child bearing, or physical characteristics to distinguish them from other members of the female sex. Dr. Robert T. Frank was kind enough to study the excretion of estrogens in all the urine passed for one month in two patients in this series (Cases 8 and 10). He was unable to detect any abnormalities in this respect.[12] A family history of thromboangiitis obliterans was searched for, but was not found in any of the twenty-five women in this series. Unless future experience shows a much greater incidence of the disease in women, it may be necessary to accept as an explanation that women do not frequently inherit the specific sensitivity to tobacco which is apparently needed to make possible the development of thromboangiitis obliterans.

All of the women in this series with thromboangiitis obliterans were habitual smokers. Progression of the disease was regularly associated with the continued or resumed use of tobacco. All patients restored to good health who have refrained from smoking have remained in excellent condition. Thromboangiitis obliterans in women, as in men, is due to the use of tobacco by persons sensitive

to this substance. The most essential part of treatment is to make sure that these patients stop smoking permanently.

Since there have been only twenty-five instances of thromboangiitis obliterans in women in over 1,600 cases of this disease seen by the writer, it is still a rare condition in the female sex. However, the occurrence of occlusive vascular disease in young women must be regarded as manifestations of thromboangiitis obliterans unless there is another obvious cause.

SUMMARY

Twenty-five cases of thromboangiitis obliterans in women are presented. The greater tendency for the disease to manifest itself in the hands of women is pointed out. The differential diagnosis between Raynaud's disease and thromboangiitis obliterans is discussed. The etiological relationship of thromboangiitis obliterans to the use of tobacco is again demonstrated.

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Clinical Reports

A CASE OF PARADOXICAL EMBOLISM

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PARADOXICAL embolism, while not rare, is relatively uncommon, as evidenced by the fact that only twelve references have been found in a search through the available literature for the period 1921 to 1945. It is also of particular interest at this time because of the extensive studies being carried on in many centers in connection with thromboembolic phenomena.

Patency of the foramen ovale is not infrequently found when it is searched for diligently. Thompson and Evans[1] reported studies conducted along these lines on 1,100 consecutive autopsies, and reported varying degrees of patency in 35 per cent of these cases. In 29 per cent, the opening in the foramen ovale would admit a probe, and in 6 per cent, it was sufficient to admit a pencil.

From this it is readily reasoned that some other factor might be operative in causing embolic material to pass from the right side of the heart directly into the arterial circulation; otherwise, the condition should be encountered much more often than it is. With these considerations in mind, the following report of a case was felt to be justified.

CASE REPORT

W. B., a 69-year-old white man, had a transurethral prostatectomy for a benign prostatic hypertrophy on Sept. 20, 1946, in the Royal Alexandra Hospital. His postoperative course was entirely satisfactory in that his temperature was not unduly elevated and subsided to normal by the fifth day. However, on the eighth day he experienced slight pain in the left calf, and when the chart was reviewed, it was noted that he had a temperature elevation amounting to 101.4°F. on that day. There was also some indication of slight pitting edema in the left leg.

He was kept at complete rest and when he received his discharge from the attending surgeon on Oct. 11, 1946, his condition was apparently quiescent. However, he had to be readmitted as an emergency within twelve hours of his leaving the hospital because of a secondary hemorrhage into his bladder.

This was followed by a febrile episode lasting about five days, during which time he was given local treatment in the form of bladder irrigations and general treatment by the administration of penicillin intramuscularly. His recovery from this was such that he was permitted to be up and about in six days' time.

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About noon on October 19, shortly after returning from the lavatory, he was found sitting on the edge of his bed, dyspenic, cyanosed, and obviously in an advanced state of collapse. He was only able to indicate intense upper abdominal pain.

A tentative diagnosis of massive pulmonary embolism was made. Measures such as the administration of intravenous heparin and papaverine were instituted at once, along with oxygen administration.

An electrocardiogram taken subsequently (Fig. 1) lent further weight to the diagnosis, as there was definite indication of acute cor pulmonale. A portable roentgenogram of the chest showed, "patchy consolidation involving both lungs, which, in view of clinical findings, could be due to massive, bilateral pulmonary embolism."

The patient lapsed into a comatose state, and he remained extremely cyanosed in spite of continuous administration of oxygen by mask. In contradistinction to what is usually noted under such circumstances, his pulse was not excessively elevated and his blood pressure did not drop as was anticipated.

The patient remained in this state for approximately fifty-one hours, when death finally took place. An electrocardiogram taken two hours before death is shown in Fig. 2.

The post-mortem examination was made eighteen hours after death by one of us (C. R.). When the thorax was opened, it was noted that both lungs were contracted to about one-half the size usually found under such circumstances. They were of a dark, livid color and exhibited almost a total lack of aeration. It seemed extremely remarkable that this patient had been able to live so long when so little pulmonic tissue was capable of its respiratory function.

The majority of the branches of the pulmonary artery were occluded with what appeared grossly to be recent ante-mortem thrombus. This, on section, was seen to be composed of laminated masses of platelets and red blood cells. The outlines of the red blood cells were clearly visible everywhere, except at the periphery of the clot where slight red cell degeneration was present and only "ghosts" of red cells were seen. There was also slight round cell and polymorphonuclear infiltration in this area. One of the larger branches of the pulmonary artery supplying the right lower lobe was found to be occluded by what appeared to be a somewhat older thrombus. This, on section, showed the typical appearance of early organizing thrombus. Red cell outlines were only occasionally visible in a mass of greyish amorphous-appearing material which showed marked infiltration with round cells, phagocytes containing blood pigment granules, and a few polymorphonuclear leucocytes. The margins of this thrombus showed infiltration with young fibroblasts. This latter finding suggested that a recent previous embolism had taken place. While the right auricle was moderately distended, the distention was not near that usually anticipated under such conditions.

On further examination of the abdominal organs, both kidneys showed recent and older areas of infarction, and both renal arteries, on careful examination, were found to contain fresh emboli. This was rather perplexing in view of the fact that a preliminary examination of the heart did not reveal any obvious cause, such as vegetations or mural thrombi, in the chambers of the left side of the heart.

A careful examination of the foramen ovale revealed an opening which was covered by a vestige of the septum primum acting as a valve flap. The free edge of this structure protruded into the lumen of the left atrium in such a way that blood could flow from the right atrium to the left, but it could be closed by any reversal of this process. The aperture covered by the valve flap would readily admit a lead pencil (Fig. 3).

Further examination revealed the presence of thrombophlebitis, involving the left deep femoral vein. In addition to this, extensive thromboses were found in the venous plexus about the prostatic bed. It seemed more likely that the massive terminal pulmonary and renal infarction must have been due to embolism secondary to the femoral thrombophlebitis.

The presence of varying degrees of organization and resolution found in the infarcted areas in both the lungs and kidneys indicated that showers of emboli must have been released some time prior to the massive terminal episode.

Date 10/19/46

I

II

III

IV

CF4

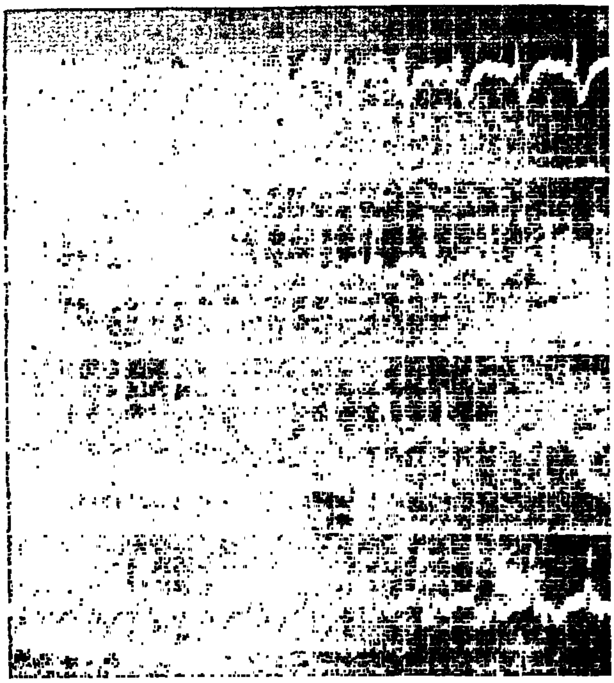

Fig. 1.—Electrocardiogram taken about three hours after the onset of the pulmonary embolism. It shows a sinus tachycardia with a rate of 124 per minute, marked S waves in Leads I and II. There are inverted T waves in limb Lead III and CF_4. In addition to this, there is a slight elevation of the S-T interval in limb Lead III.

Date 10/21/46

I

II

III

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CF4

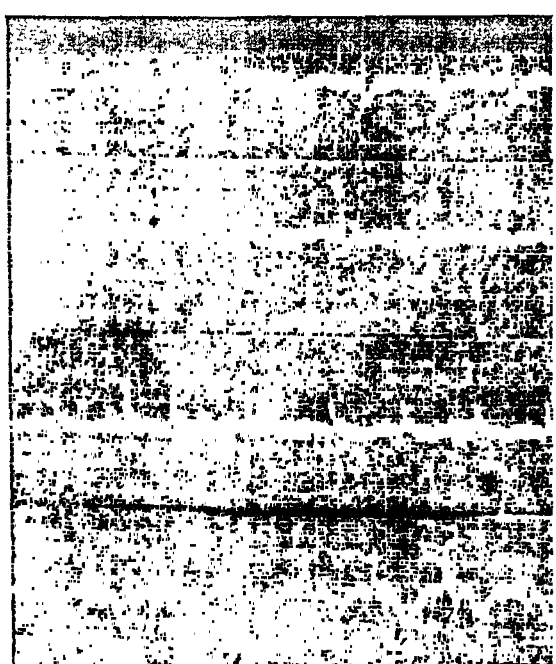

Fig. 2.—Tracing taken approximately two hours before the patient suddenly expired. The rate is 116. There is a sinus tachycardia with a rate of 116 per minute and occasional premature auricular contraction. S waves are still present in Leads I and II, but not to as marked an extent as in the preceding tracing. The T waves are negative in Lead III. There is a marked negative T wave in CF_4. The same slight elevation of the $S\text{-}T_3$ persists without any reciprocal change seen in $S\text{-}T_1$.

Fig. 3.—A view of the foramen ovale from the right auricular side showing closure of the valve flap by pressure from the left atrial side, simulating a condition normally found where the patent foramen ovale is protected by a valve flap derived from a vestige of the septum primum. There is no increased right atrial pressure present. The arrow points to closed valve flap covering the patency in the foramen ovale.

DISCUSSION

Apart from the fact that there was a patent foramen ovale in this case, two other interesting features deserve recognition and analysis: The first is the probability that pulmonary embolism was a precipitating factor in forcing embolic matter through the foramen; the second is that this individual lived much longer than would have been anticipated after having sustained such a massive pulmonary embolism.

The first of these considerations is not an original observation, as Wittig,[2] in 1927, noted that 50 per cent of the cases of paradoxical embolism were associated with preceding pulmonary embolism. This is readily explained by the sudden rise of pressure in the right atrium, as a result of obstruction in the pulmonary artery and its branches, which is presumably great enough to force open the valve flap of the foramen ovale. In this way, embolic material could be forced directly into the left atrium and thus pass into the systemic circulation. It is quite apparent that such a mechanism must have been operative here.

Visscher[3] has established the important role which the Thebesian system of veins plays in the return flow of the coronary blood in the right atrium and ventricle. He has also indicated how this renders the right side of the heart particularly vulnerable to increased intra-atrial and intraventricular pressure. It is reasonable to assume that in this case the patent foramen ovale acted as a safety valve. In this way, the function of the Thebesian system was not disturbed as it might have been if no opening existed in the intra-atrial septum.

In the average case of massive pulmonary embolism, Currens and Barnes[4] have expressed their belief that one of the main causes of death is impairment of the coronary circulation to the right heart. This is due to the rise of pressure in the right atrium which decreases the pressure gradient in the coronary circulation.

Thompson and Evans[1] comment on the fact that one of their patients survived pulmonary embolism for forty-eight hours in the presence of a patent foramen ovale. They did not elaborate on this, however.

Fig. 4.—A view of the foramen ovale from the right side showing opening of the valve flap by pressure from the right atrial side, simulating the condition arising in the presence of increased right atrial pressure. A medium-sized pair of thumb forceps is inserted in the opening, showing the degree of patency of the foramen ovale.

In this case, it appeared rather remarkable that life could have been maintained for fifty-one hours when so little functioning lung tissue remained. The evidence accumulated in this case would seem to indicate that patency of the foramen ovale, under these conditions, might serve to increase the pressure gradient in the coronary circulation of the right side of the heart. This would seem to be a reasonable explanation as to why this individual lived as long as he did after such massive pulmonary embolism.

SUMMARY

1. A case of paradoxical embolism is presented.
2. Its relationship to pulmonary embolism is indicated.
3. An explanation for the unusual prolongation of life in this case is suggested.

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EXTREME BRADYCARDIA

Report of a Case Exhibiting a Ventricular Rate of Less Than Twelve per Minute

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THE recognition and description of interference in auriculoventricular conduction is not a matter of recent observation, for Galen in 130 A.D. commented on this condition.[1] Heart block of some type or degree is a common occurrence. A sustained rate below 15 beats per minute, however, rarely has been observed, only three such cases having been reported in the past two decades.[2,3,4] Of these, only Ruggiero,[4] in 1937, recorded the bradycardia electrocardiographically. The patient was a 53-year-old white man whose ventricular rate shortly prior to death varied between 10.8 and 20 beats per minute, and whose auricular rate ranged between 79 and 88 per minute.

It is our purpose to report a case in which heart block produced an unusually slow cardiac rate associated with the Stokes-Adams syndrome. As far as we have been able to discover, this patient exhibited the slowest ventricular rate ever recorded by the electrocardiograph in man.

CASE REPORT

B. D., a 69-year-old Russian-born white man, was admitted to the private service of one of us (J. C. D.) on March 16, 1947, with the chief complaint of shortness of breath which had existed since Feb. 25, 1947, at which time he began to note rather severe dyspnea on exertion followed by regular attacks of paroxysmal nocturnal dyspnea. On March 6, 1947, he was aware of considerable ankle edema. The dyspnea grew progressively worse, and the patient was referred to the Jewish Hospital for study.

At the initial examination the patient appeared to be somewhat younger than his stated age. His temperature was 98° F.; the pulse and respiratory rates were 36 and 24 per minute, respectively. The systolic blood pressure was greater than 260 mm. Hg, the diastolic pressure, 90. There was slight weakness of the right side of the face which the patient claimed had been present for many years. The neck veins were markedly distended. On examination of the chest, fremitus was decreased, the percussion note impaired, and breath sounds diminished over the lower portion of the right hemithorax, posteriorly. The heart was moderately enlarged, the apex beat being palpated about 2.0 cm. to the left of the mid-clavicular line. The ventricular rate was very slow, 36 per minute, and the rhythm was regular. The systolic sounds were of good quality; no murmurs were heard. The second pulmonic sound was greater than the second aortic sound. The abdomen was flat and there was no tenderness. The liver was palpated about 2.0 cm. below the costal margin. There was edema of the arms, thighs, legs, and ankles.

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The original examination of the urine showed a pH of 7.5, specific gravity of 1.021, and 4 plus albumin. Examination of the blood showed 15.9 Gm. of hemoglobin, 5,410,000 erythrocytes, 14,450 white blood cells, and a normal differential count. An electrocardiogram on admission confirmed the presence of a marked bradycardia (34 per minute) and revealed a 2 : 1, and sometimes a complete heart block, as well as definite evidence of a healed anterior myocardial infarction.

Because of the evidence of congestive heart failure and the marked hypertension, 200 c.c. of blood was removed rapidly. At 12:30 A. M. on the day of admission the patient was seen in a typical attack of nocturnal dyspnea. His color was grey, dyspnea was severe, and the thorax was filled with loud asthmatoid wheezes. Prompt relief followed the use of aminophyllin, intravenously, and morphine sulfate and atropine sulfate, subcutaneously. Later that morning digitalization (digitoxin) was begun and general supportive therapy continued. On the third hospital day 800 c.c. of a clear, yellow transudate was removed from the right hemithorax.

A Fishberg urinary concentration test revealed a fixed specific gravity, the urine containing many granular and hyaline casts. An electrocardiogram revealed complete heart block with a ventricular rate of 28 and an auricular rate of 60 per minute. In addition, there was evidence of block of the right bundle branch. The condition improved and on March 30 the patient was breathing comfortably without oxygen and was allowed to sit on the side of the bed. Cardiac auscultation revealed a rate of 30 per minute. The sounds were still of good quality and in diastole a third distant sound was heard, which was believed to be produced by the auricular contraction. An attempt to speed the ventricular rate by means of the oral administration of atropine sulfate, grain 1/200 three times per day, was unsuccessful.

On April 1, 1947, at 10 A. M., the patient vomited, had mild twitching of the face, and became apneic and cyanotic. He was ashen grey and perspiring profusely, but still well oriented and had no motor or sensory paralyses. Oxygen therapy was reinstituted and caffeine with sodium benzoate was given subcutaneously. Three times in the following six hours, when the oxygen mask was removed, the patient exhibited the following phenomena: the face became florid, the eyes rolled upward and outward, there were twitchings of the facial muscles, a slight pinkish froth was seen at the mouth, and the respirations became weak and shallow. During the last of these three attacks, it was noted that the blood pressure had dropped to 170, systolic, and 60 to 70, diastolic, and that the pulse rate at the apex, as well as in the peripheral vessels, was 14 to 16 per minute. An electrocardiogram showed a ventricular rate of 12.5 to 13 per minute with an auricular rate of 50 per minute, left axis deviation, and a prolonged QRS complex (0.14 second) suggesting left bundle branch block as well as complete A-V heart block (Fig. 1,*A*).

The digitoxin was discontinued after a total of 2.4 mg. had been given in a period of fifteen days. Caffeine with sodium benzoate, grains 40; strychnine sulfate, grain 1/10; and ephedrin sulfate, grains 2¼ (grain 3/8 every fourth hour for six doses) were administered in a period of twenty-four hours. Of these, only ephedrin definitely produced acceleration of the ventricular rate.

The following morning the patient appeared to be improved, the cardiac rate having returned to 36 per minute. On only one occasion did he exhibit any further manifestations of the Stokes-Adams syndrome. An electrocardiogram taken late that afternoon revealed a ventricular rate of 34 per minute, an auricular rate varying between 62 and 85 per minute, and a prolonged QRS complex (0.12 second) with a suggestion of right bundle branch block (Fig. 1,*B*).

At 8 A. M., April 4, the patient became semistuporous, and when he was seen, the radial and apical pulses were approximately 8 per minute. A single lead (CR_4) of an electrocardiographic tracing taken at 10 A. M. showed a rate between 11 and 12 per minute (Fig. 1,*C*). Convulsive seizures became more frequent. At 12 noon, in spite of therapy, the radial and apical rates were between 8 and 10 per minute. An electrocardiogram taken between 12:20 and 12:40 revealed a ventricular rate averaging 9.8 per minute and an auricular rate of 110 per minute (Fig. 1,*D*). Five minutes later, with the electrocardiograph still running, in spite of an intracardiac injection of adrenalin, the heart action ceased and the patient was pronounced dead (Fig. 1,*E*).

Post-Mortem Examination.—Post-mortem examination was performed approximately four hours after death by Dr. Leonard L. Malamut. The pleurae were obliterated by old, dense adhesions. There was a small, loculated effusion in the interlobar fissure on the right. The vessels

showed some atherosclerosis, especially the abdominal aorta. There were small cysts approximately 5 cm. in diameter containing clear fluid scattered throughout the parenchyma of both kidneys. The remainder of the organs, with the exception of the heart, showed no changes of any importance.

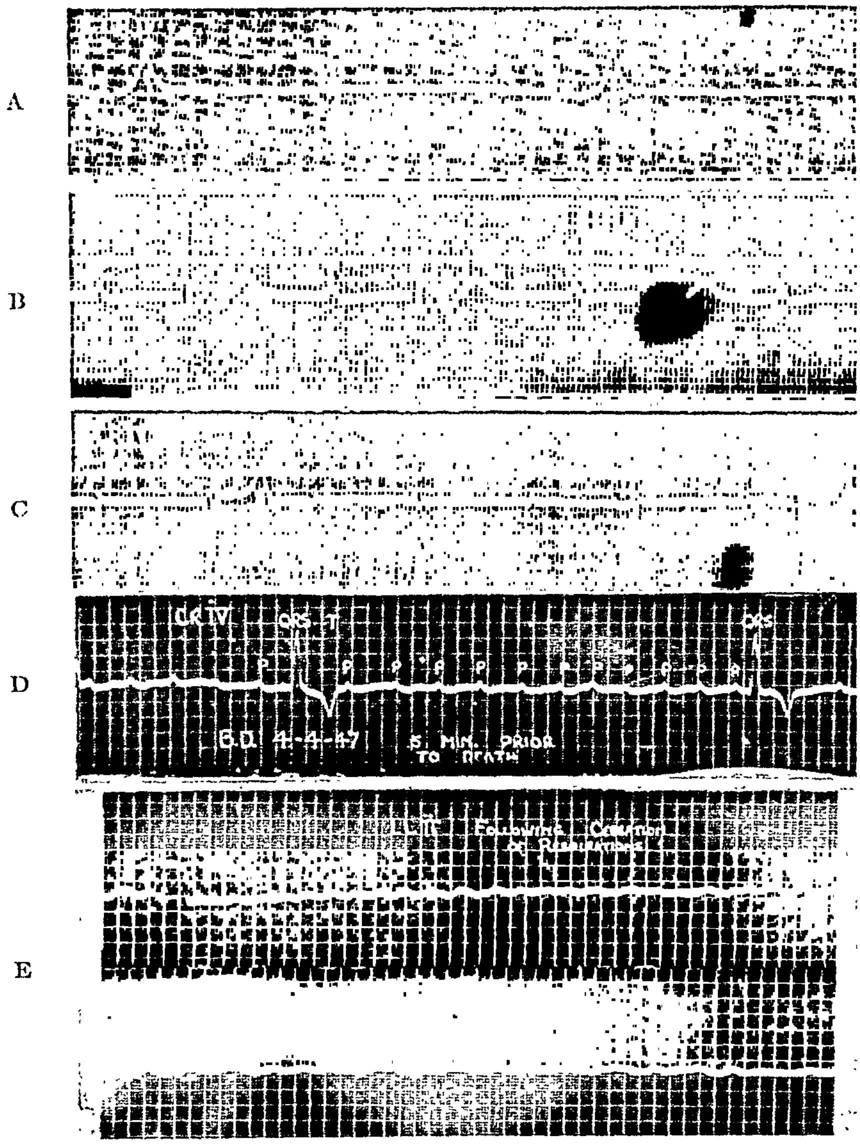

Fig. 1.—A series of electrocardiograms taken *A*, three days before death (ventricular rate, 12.5, auricular rate, 50); *B*, two days before death, af er oral administration of ephedrin sulfate (ventricular rate, 34); *C*, three hours before death (ventricular rate, 11.5); *D*, five minutes before death (ventricular rate, 9.8); *E*, following cessation of respirations.

All tracings are lead CR_4; other leads are omitted. *D* and *E* taken with paper running at higher speed.

In situ, the heart appeared to be moderately enlarged. It weighed 420 grams. The color and tone of the myocardium were exceptionally good, and there was no gross evidence of any involvement of the septum or wall of the left ventricle. The tricuspid and mitral valves were normal for the age of the patient, but there was slight fibrosis of the valvular rings. The pulmonic valve was normal, and the cusps of the aortic valve showed a minimal amount of fusion. The endocardium appeared normal throughout and there were no gross abnormalities of the auriculoventricular node or of the bundle of His. Both coronary arteries showed a moderate amount of atherosclerosis for the first 5 to 6 cm., but the lumina remained completely patent to the smallest ramifications. A small accessory coronary vessel arose at the mouth of the right coronary artery from the anterior sinus of Valsalva.

Microscopic examination of the heart muscle, per se, revealed no definite pathologic changes except some hypertrophy of the wall of the left ventricle. Special serial sections were made of the bundle of His and stained by hematoxylin and eosin as well as by the Mallory trichrome technique. In an area just below the membranous septum, distal to the bifurcation of the bundle, there was found a plaque of calcific deposit with a maximum diameter of 0.5 mm. (Fig. 2), around which there was a large amount of collagenous material. In the anterior portion of one section this calcification involved chiefly the right bundle branch, and in the posterior portion, the left bundle branch. As the sections progressed it became obvious that most of both bundles were involved, as evidenced by the increase in vacuolization of the cells comprising the Purkinje fibers, and finally, almost complete necrosis of these cells. A section through the A-V node also revealed small calcific deposits involving some cells of the conduction system (Fig. 3).

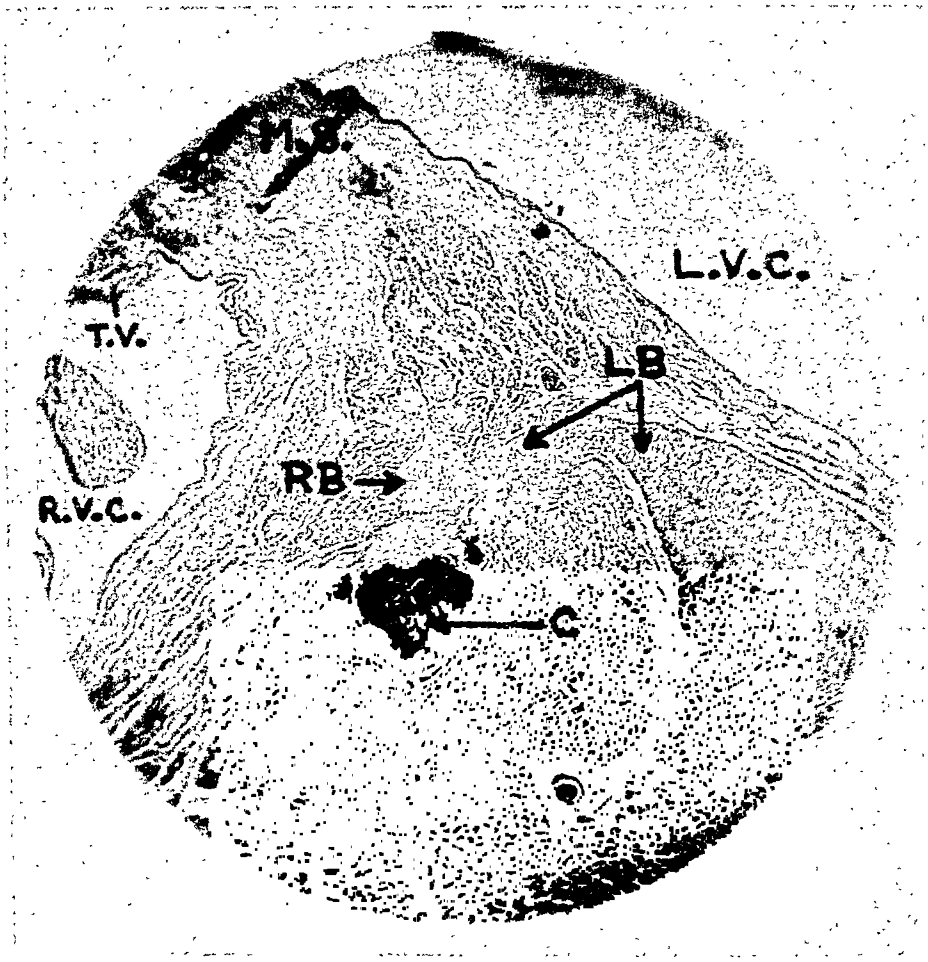

Fig. 2.—Section through interventricular septum showing large calcific plaque (C) involving most of the right bundle (*R.B.*) and a very small portion of the left bundle (*L.B*). *T.V.* designates the tricuspid valve; *R.V.C.*, the right ventricular cavity; *L.V.C.*, the left ventricular cavity; *M.S.*, the membraneous portion of the interventricular septum. × 37.5.

DISCUSSION

The exact etiology of the complete heart block in this patient was in doubt until careful histologic examination was made of serial sections of the conduction system. No gross occlusive process was found in any of the coronary vessels; indeed, the lumina of these vessels were unusually large and their endothelial

surfaces surprisingly free of atherosclerosis, considering the patient's age. Perhaps the adequacy of the blood supply to the heart muscle itself accounted for its ability to maintain the minute cardiac output at a volume which was consonant with life.

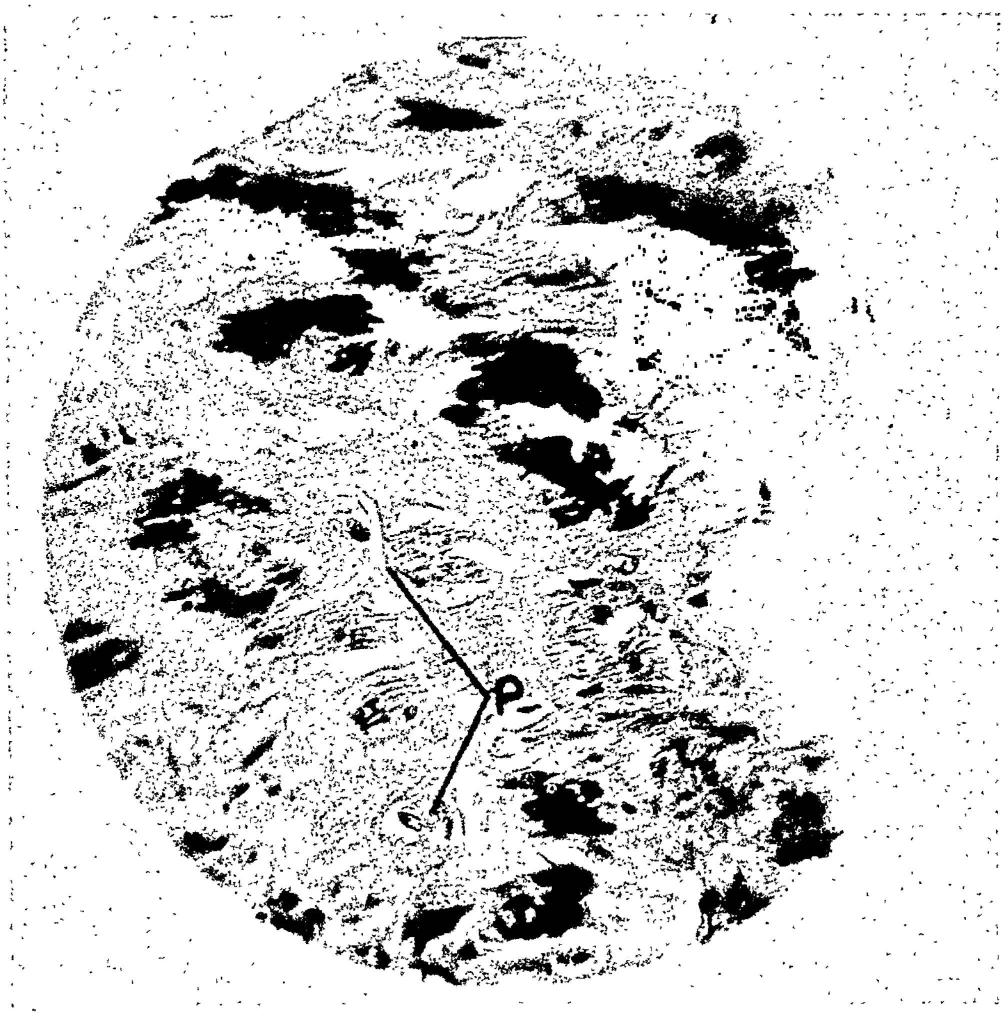

Fig. 3.—Section from area of A-V node exhibiting small calcific areas (heavily stained portion) and paucity of normal cells of the conduction system (*P*). × 400.

The many causes of heart block are well known. Arteriosclerosis, predominant among these, accounted for 62 per cent of Willius' series of thirty-seven cases.[5] Intrinsic heart disease, endocrine disturbances, digitalis, malignancies, chemical poisoning, anaphylaxis, and various infections have been found at one time or another to be the underlying pathologic condition in heart block. Notwithstanding the diversity of etiology, pathologic changes in complete heart block remain obscure in about 10 per cent of cases. In the case reported, calcific deposits, so situated that they could have been partially or wholly responsible for the conduction defect present, furnished an adequate pathologic explanation of the A-V heart block.

Of all the methods of treatment described, including the use of strychnine, atropine, barium chloride, and ephedrin sulfate, the last of these was the only one which seemed to afford some temporary relief to our patient.

SUMMARY

1. A patient with complete heart block whose ventricular rate during the last twelve hours of his life varied from 12.5 to 9.8 beats per minute has been presented.

2. The probable causative pathologic factor in this case was shown to be calcific deposits involving the A-V node and the right and left branches of the bundle of His.

3. It appeared that ephedrin was a useful drug in increasing the ventricular rate and in lessening the frequency of the Stokes-Adams syndrome.

4. This is apparently the slowest sustained heart rate recorded electrocardiographically in man.

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Abstracts and Reviews

Selected Abstracts

Schmidt, E. C. H.: Virus Myocarditis. Pathologic and Experimental Studies. Am. J. Path. 24:97 (Jan.), 1948.

A virus isolated in 1945 by Helwig and Schmidt from the myocardial lesions of anthropoid apes dying from interstitial myocarditis was found consistently to cause myocardial lesions in mice.

Three apes died, two very suddenly, after exposure to many human visitors. The pathology was strikingly the same in all. A virus was cultured after inoculation of ground spleen into mice. The hearts in all three apes were markedly dilated and on section showed greyish semi-softened areas. Bilateral hydrothorax and a marked hemorrhagic pulmonary edema indicated both subacute and acute congestive failure. Microscopic examination showed extensive necrosis and diffuse round-cell infiltration. Fragmentation and loss of myocardial fibrils was accompanied by inflammatory infiltration of mononuclear and polymorphonuclear cells.

The etiological agent was not looked for in one of these cases of virus myocarditis; it was not found in another case; but in one case the pleural fluid and a splenic extract caused fatal paralysis of the hindquarters in a group of ten mice. Various visceral extracts from these ten mice caused, in turn, a frequently fatal paralysis in a second group of ten mice. Extracts of viscera from this batch of mice and the original fluids were inoculated into other mice, and ten successful mouse passages were made before loss of potency occurred. The mice so inoculated showed a characteristic paralysis on the fourth day, and most of them died on the seventh to the tenth day.

The cardiac lesions in these mice consisted essentially of focal necrosis of the myocardium with monocytic infiltration of the surrounding areas. Interstitial edema and diffuse interstitial cellular infiltration, both monocytic and polymorphonuclear, appeared throughout the myocardium. In those animals surviving until the twelfth day, calcification of the necrotic foci was noted, and after twenty days, this calcification plus fibroblastic replacement were the only remnants of the myocardial disease.

Guinea pigs, to a large degree, and rabbits, to a lesser degree, showed the same myocardial changes in response to inoculation of this virus.

Control animals failed to show any cardiac lesion similar to this type of virus myocarditis. Likewise, sera from patients suffering from rheumatic fever and influenza did not produce lesions of interstitial myocarditis in mice. Mice that had been placed as controls in the same cages as the inoculated animals did not contract the disease.

Intravenous, intraperitoneal, and subcutaneous inoculation, using visceral extracts in acitic fluid-saline suspension, were dependable for the production of the specific myocarditis. Sera of mice that had recovered from the paralysis, when combined in the same inoculum with potent visceral extracts, nullified the action of the latter, thus exhibiting a true antibody action.

While the myocardial lesion of "anthropoid virus disease" duplicates to a remarkable degree human myocarditis associated with various types of virus disease, the authors are reluctant to identify it with human pathology because of their inability to identify this virus with any of the known viruses; also because of the apparent freedom from infection shown by laboratory workers who handled the sick apes.

GOULEY.

Scheinker, I. M.: Alterations of Cerebral Capillaries in the Early Stage of Arterial Hypertension. Am. J. Path. 24:211 (Jan.), 1948.

Scheinker, continuing his previous studies on the association of arterial hypertension with cerebral vascular disease, describes in this report the early stage of cerebral vascular degeneration with reference especially to changes in the cerebral capillaries. The study was based on findings in six fatal cases of arterial hypertension in which death occurred one to two years after the onset of the disease. However, only two cases are reported in detail.

The first case showed characteristic arteriolosclerosis featured by petechial hemorrhages in the pleura and kidneys. The vessels of the circle of Willis showed a definite arteriosclerosis. There was a small pontine hemorrhage and, in addition, a diffuse swelling of the midbrain with loss of demarcation between gray and white matter.

Microscopically, the important vascular changes were found to be in the capillaries. They exhibited a uniform pathologic process, showing in combination extreme cellular thickening with degenerative alterations of their walls. The thickening was due to a fibroblastic proliferation of the adventitia and hyperplasia of the lining endothelium. Also, there was a pericapillary increase of glial nuclei due to glial hyperplasia in the surrounding nervous tissue. The degenerative changes consisted of a homogeneous thickening of the wall with narrowing and almost complete obliteration of the lumen. Some of these tiny vessels were converted into structureless hyalinized nodules surrounded by glial hyperplasia. The arterioles showed only a moderate degree of thickening and hyalinization. The cerebral veins, however, showed definite changes, there being marked distention of these vessels and degeneration of their walls, even in branches remote from the area of brain hemorrhage. The degeneration of the venous wall also consisted of a structureless, homogeneous, apparently hyaline infiltration. The white matter showed marked increase of fluid content. The perivascular spaces were prominently distended throughout. Scheinker describes the venous changes as those of vasoparalysis.

The second case was that of a patient who died during the course of a Smithwick operation. This case, like the first, showed arteriolonephrosclerosis. Sections throughout the midbrain revealed diffuse swelling of the tegmen of the pons, with almost complete obliteration of lumen of the fourth ventricle.

Again, the striking histologic findings were confined to the capillaries, which showed fibroblastic proliferation of the adventitia and hyperplastic thickening of the lining of the endothelium. Also, aside from the endothelial change, a structureless hyaline thickening of the vessel wall was noted, with narrowing or complete obliteration of the vascular lumen. On the other hand, the arterioles were only slightly affected.

This report points out that an important capillary degeneration constitutes, at least in some cases, the earliest and most accelerated type of vascular change in malignant hypertension. Although the two cases described showed characteristic renal vascular changes, Scheinker feels that in the entire group no direct parallelism could be established between the renal and cerebral developments. In some cases the cerebral vascular changes were clearly predominant.

GOULEY.

Prinzmetal, M., Ornitz, E. M., Simkin, B., and Bergman, H. C.: Arterio-venous Anastomoses in Liver, Spleen and Lungs. Am. J. Physiol. 152:48 (Jan.), 1948.

Glass spheres ranging in diameter from 10 to 440 μ were injected into afferrent vessels of liver, spleen, and lungs of anesthetized rabbits, cats, and dogs. The spheres were recovered from the venous circulation of all organs. This demonstrates the presence of direct arteriovenous communications because the diameter of the glass spheres definitely exceeded that of capillaries. The results are similar to those reported by the authors for the heart and kidneys and suggest that such routes may be available in all organs. The physiologic significance of such short circuits remains unknown.

HECHT.

Mullick, D. N., Alfredson, B. V., and Reineke, E. P.: Influence of Thyroid Status on the Electrocardiogram and Certain Blood Constituents of the Sheep. Am. J. Physiol. 152:100 (Jan.), 1948.

The normal electrocardiogram of nine sheep (Lead II) reveals an average heart rate of 112 (88 to 142) per second, a P-R interval of 0.102 (0.08 to 0.14) second, QRS of 0.038 (0.02 to 0.04) second, and a Q-T interval of 0.271 (0.22 to 0.32) second. Bazzett's K value measured 0.367.

Thyroidectomy resulted in a decrease in heart rate and flattening of T which readily reverted to normal upon administration of thyroprotein (1 to 2 mg. per 45 kilograms of body weight). Thiouracil administration resulted in a moderate decrease of heart rate and a paradoxical increase in the height of the T wave. Serum fat levels (Allan) changed little following thyroidectomy and thyroprotein administration. They rose sharply upon administration of thiouracil. No changes could be demonstrated at any time in blood hemoglobin content, serum protein, calcium, phosphorus, or magnesium.

HECHT.

Taylor, H. L., Henschel, A., and Keys, A.: Cardiovascular Response to Posture and the Problem of Faintness and Syncope in the Semi-starved Individual. Am. J. Physiol. 152:141 (Jan.), 1948.

Thirty-one men were kept on a controlled regimen of activity for six months on a diet of 1,658 calories. This resulted in semistarvation similar to that induced by dietary restrictions of civilian populations in Western Europe during World War II. The subjects lost 24 per cent of their body weight. The cardiovascular effects of posture were studied by the use of a tilting table. Pulse rate, blood pressure, and pulse pressure were reduced in both the horizontal and tilted position. The increase in heart rate and fall in pressure observed as the result of tilting during the control period were found to remain unaltered during the semistarvation period. In the control period four men fainted during ten minutes of tilting. All four withstood ten minutes of tilting during the starvation period. Faintness and dizziness upon arising or unassociated with postural changes were almost universal complaints during the experimental period. It appears that such subjective sensations, together with "blackouts" and "light headedness" during such states, cannot be ascribed to circulatory incompetence.

HECHT.

Roth, G. M., and Sheard, C. H.: Maintenance of Vasodilation of the Extremities of Normal Individuals for a Prolonged Period by the Ingestion of Two to Four Substantial Meals in Close Succession. Am. J. Physiol. 152:183 (Jan.), 1948.

It was demonstrated in twenty-four normal persons (fifty-two observations) that the rise in skin temperatures of the extremities was greater and could be maintained for about one hour longer after the ingestion of three meals than after one or two meals. An additional two hours of vasodilation were obtained after the ingestion of four meals of 500 to 800 calories taken at two-hour intervals. The rate of sweating and the initial basal metabolic rate obviously modulated the results obtained.

HECHT.

Klemperer, P.: The Pathogenesis of Lupus Erythematosus and Allied Conditions. Ann. Int. Med. 28:1 (Jan.), 1948.

The original view of the author was that the coexisting endocardial, vascular, serosal, and joint involvement of acute lupus erythematosus must be the manifestation of a primary injury of the endothelial cells and that the disease could be explained as the result of the action of an endotheliotropic injurious factor. Since then, the author has been able to show the presence of a widespread alteration of the connective tissue as well as the endothelium in this disorder. This connective tissue disturbance affects the heart, serous membranes, vasculature, lymph nodes, skin, and mediastinal and retroperitoneal areas. The morbid process becomes manifest in focal fibrinoid metamorphosis of the collagenous fibers, resulting occasionally in fragmentation of these

elements and in swelling and increased density of the interfibrillar homogeneous ground substance which normally is almost invisible. Such foci are more or less heavily infiltrated by polymorphonuclear leucocytes and lymphocytes. The fixed connective tissue cells, fibroblasts, and histiocytes, while increased in number, almost invariably show evidence of decay, such as pyknosis and nuclear fragmentation. The alteration of the glomerular capillaries (wire loops and focal necrosis) is conspicuous in acute lupus erythematosus. Another microsocopic featuie present with conspicuous frequency was sclerosis of collagen fibers around the follicular arteries of the spleen. This lesion also reflects a fundamental alteration of the connective tissue though of a nature different from fibrinoid metamorphosis.

The author believes that acute lupus erythematosus is defined anatomically as a disease characterized by a fundamental alteration of the collagenous portion of the connective tissues. In this respect, acute lupus erythematosus shares a common element with generalized scleroderma, rheumatic fever, and even periarteritis nodosa. The author, however, is unwilling to accept a common pathogenesis for this entire group of diseases. He devotes a large portion of the paper to a consideration of the possible causes for such tissue alterations in acute lupus erythematosus and to speculation concerning the fundamental physicochemical disturbance responsible for the changes in the structure of the "ground substance." The role of allergy in the causation of the lesions of disseminated lupus erythematosus is not considered an important one by the author.

WENDKOS.

Humphreys, E. M.: The Cardiac Lesions of Acute Disseminated Lupus Erythematosus. Ann. Int. Med. 28:12 (Jan.), 1948.

The cardiac lesions in twenty-one authentic cases of acute disseminated lupus erythematosus are analyzed. Endocardial lesions were found in twelve cases. Save for the bulkier lesions affecting two, three, or four valves (observed in seven cases), endocardial lesions were easier to recognize in microscopic sections than they were grossly.

Some focal myocarditis was encountered in most of the twenty-one cases. More significant were: the fine scars, like those of small infarcts; the increased density of collagen along many or most of the intermuscular septa; the thickened small arteries. Myocardial lesions of these types were found beneath the more extensive mural vegetations or near partially or completely occluded arteries. Also there were acute exudative reactions, not easily interpreted. Fresh fibrinoid necrosis of collagen or of vessel walls was easily demonstrable in the more severe cases. In a considerable number of hearts, there was marked loosening of the fibrous substance, producing an edematous appearance not unlike that seen in the beriberi heart. In several, severe fatty degeneration of myocardial fibers was noted. In a number of patients, there were no changes other than interstitial edema, atrophy of fatty tissue, and the presence of dense collagen and a few round cells near the epicardial surface.

In nine cases a serofibrinous pericarditis was present, and in five of these (all with nephritis), there were effusions of 600 to 950 cubic centimeters. In six cases the pleural space was obliterated by loose gelatinous fibrous adhesions. Within these adhesions there were foci of fresh necrosis or of fibrinous and cellular exudation.

In proportion to the wasted state of the bodies of these patients, the cardiac weights were usually normal or slightly increased. In the patients who had nephritis for a sufficient period, weights of 350 to 450 grams were observed. The larger hearts were found in patients whose nephritic symptoms had been present long enough for hypertension to develop.

WENDKOS.

Massey, F. C., and Walker, W. J.: Complete Atrioventricular Block in Diphtheritic Myocarditis. Arch. Int. Med. 81:9 (Jan.), 1948.

A detailed analysis is made of a complex arrhythmia with complete atrioventricular block and a progressively decreasing ventricular rate occurring in a case of hypertoxic tonsillopharyngeal diphtheria in a 17-year-old white boy. Serial electrocardiograms reflected directly the lesions produced by the disease as observed at autopsy. The fact that the atrial musculature was less

severely impaired than the ventricular accounted for the progressively diminishing ventricular rate despite a relatively constant atrial rate. The serious impairment of the conducting system was the prime basis for the advent of complete heart block and prior intraventricular block. The major microscopic pathology was extensive myocarditis with edema and notable degenerative changes. Occasional cellular accumulations in the periatrioventricular nodal region was so dense that it simulated abscess formation.

BERNSTEIN.

Hendry, W. G.: Superior Mesenteric Arterial Occlusion—Recovery Without Resection. Brit. M. J. 1:144 (Jan.), 1948.

The incidence of spontaneous recovery is impossible of assessment from data available, as a number of patients, whose cases are undiagnosed and untreated, will recover. The pathology is always one of thrombosis or embolism with severe associated vasospasm. The author reports the case of a 64-year-old retired bank clerk who was seized with severe abdominal colic followed by nausea and vomiting. Examination found him cyanotic with a pulse rate of 120 and a blood pressure of 70/50. There was no rigidity or distention of abdomen, but generalized tenderness was present. A laparotomy was performed. The two upper loops of jejunum were in a condition of hemorrhagic infarction and seemed still viable. The abdomen was closed without intervention. Postoperatively, continuous gastric suction, intravenous fluids, and 50 mg. of heparin, intravenously, every five hours, were given. On the fifth day the patient was quite well and was able to take a normal diet. Heparin was discontinued. The patient made an otherwise uneventful recovery.

WAGNER.

Cox, N.: Cardiac Murmurs in Infancy. Brit. M. J. 1:148 (Jan.), 1948.

Opinion varies concerning the significance of murmurs heard in infancy. Six hundred thirty ostensibly healthy children enrolled in the Child Health Survey of the Institute of Social Medicine formed the basis of this study. Thirty-two (5 per cent) were found to have systolic murmurs. No diastolic murmurs were heard. Some murmurs were present at the first examination (before the sixth week) and later either disappeared or persisted. Others appeared for the first time at the second or subsequent examination; some of these disappeared or persisted. In twenty-two cases the murmur was not detected until the age of 9 months.

This is a preliminary report on a study which the author plans to continue. These children will be available for observation throughout life, and it is hoped this study will shed light on the significance, progress, and development of these children and their murmurs.

WAGNER.

Steinmann, V. B., Ludi, H., and Barben, H. P.: Circulatory Investigations Resulting From Drugs Which Paralyze the Sympathetic System. I. Ergotamine (Gynergen). Helvet. med. acta 15:76 (Jan.), 1948.

1. In this study the effect of ergotamine (Gynergen) on the circulation of the healthy human subject was investigated. Ergotamine was administered in varying doses subcutaneously (0.05, 0.1, 0.25, and 0.5 mg.). The changes in the circulatory dynamics were examined after the method of Wezler and Boger .dynamics of the heart after the method of Blumberger. Electrocardiograms were registered simultaneously.

2. The following typical effects on the circulation could be shown: slowing of the pulse rate, increase in the diastolic blood pressure, decrease in the pulse pressure, usually a moderate rise in the systolic pressure, small increase in the pulse-wave velocity and the elastic resistance of the elastic cavity organs ("Windkessel") (only with higher doses), and a definite decrease of the buffer factor of the arterial system. Furthermore, the beat and minute output, and sometimes the peripheral resistance were markedly increased. The tension interval was always shortened as was the expulsion interval, the latter, though, to a very moderate degree only. The electrocardiogram showed minor changes in isolated instances only, mostly a flattening of the P wave and a slight increase of the T wave and the conduction interval.

3. The circulatory effect of ergotamine in the human subject shows itself, therefore, to be opposite to that of adrenalin. The fact that in spite of this, both substances can lead to a rise of the arterial pressure-average, is explained on the basis of the observed circulatory changes. It therefore becomes evident that the changes in blood pressure alone do not indicate accurately enough the effects of a circulatory-active substance.

4. Ergotamine acts without doubt peripherally, that is, on the vessels, on the one hand; on the other hand, the great likelihood exists that, up to a certain degree, a direct antiadrenergic action on the heart is also present.

AUTHORS.

Spuhler, V. O., Wiesinger, K. and Meili, E.: Diuretic and Circulating Plasma Volume. Helvet. med. acta 15:95 (Jan.), 1948.

1. Geigy-blue 536 is suitable for the determination of circulating blood plasma.
2. Our normal values for the circulating plasma volume of 1,800 to 3,800 c.c. correspond to those of the literature.
3. After the administration of Salyrgan the amount of circulating plasma was reduced in every case and the hematocrit was increased in five of six cases. These results may be due to a concentration of blood; this explanation coincides with the assumption that mercurial diuretics have their exclusive site of action in the kidneys and draw water from the blood.
4. Xanthine derivatives have their special site of action in the circulatory system.
5. In some cases of anasarca and diabetes, we observed that the dye disappeared more rapidly than usual from the blood, probably because of a greater capillary permeability. The dye is found regularly in artificial wheals produced by histamine.

AUTHORS.

Makinson, D. H., Oleesky, S., and Stone, R. B.: Vitamin E in Angina Pectoris. Lancet 1:102 (Jan. 17), 1948.

It has been suggested that vitamin E relieves the pain and improves the exercise tolerance of patients with angina pectoris by its possible action as a coronary vasodilator or by virtue of a beneficial influence on myocardial metabolism.

The authors' series included twenty-two patients (seventeen men and five women), 44 to 66 years of age, who were having frequent attacks of angina. The patients received the following drugs successively: 50 mg. of vitamin E three times daily, phenobarbital, grain ½ three times daily, aminophylline, grains 1½ three times daily, and calcium lactate, grains 5 three times daily (as a control). After each drug had been received for three weeks, the effects were evaluated. The results of this study suggest that vitamin E is no more beneficial than phenobarbital or aminophylline; the authors conclude that vitamin E is not of any therapeutic value in the routine treatment of angina pectoris.

WAGNER.

Godfrey, J.: Thoracic Tenderness in Pulmonary Infarction. New England J. Med. 238: 86 (Jan. 15), 1948.

Marked, localized intercostal tenderness was observed as an early sign in five cases of pulmonary infarction. None of the cases showed the entire combination of symptoms and signs that generally are considered typical of this condition. It is suggested that chest tenderness in connection with a pleuritic type of pain, in the absence of trauma, be considered suggestive of pulmonary infarction, even in the absence of supporting symptoms, signs, or x-ray changes.

KAY.

Altschule, M. D., and Tillotson, K. J.: Mechanisms Underlying Pulmonary and Cardiac Complications of Electrically Induced Convulsions. New England J. Med. 238:113 (Jan. 22), 1948.

Maximal forced expiration with extreme diaphragmatic elevation is maintained throughout an electrically induced convulsive seizure. Profuse salivation and excessive bronchial secretion are

accompanying features. In the vigorous inspiration that terminates the seizure, aspiration of this material may result in patchy atelectasis. If this persists and becomes infected, lung abscess may develop. By a similar mechanism, latent tuberculosis may be disseminated.

Rise of peripheral venous pressure was consistently observed. This is attributed to increased intrathoracic pressure. As a result of the rush of impounded blood into the heart in the postconvulsive phase, and because an accumulated oxygen deficit must be overcome, heart work is increased. The myocardial infarctions reported in relation to electric shock therapy probably occur shortly after, rather than during, the convulsion. The authors agree with others that the arrhythmias of the postconvulsive period are probably consequent to vagal reflexes activated by sudden distention of the auricles and great thoracic veins.

D-turbocurarine is recommended to reduce the postconvulsive cardiac strain. Attention is directed to the potentially dangerous vagal stimulating effects of certain other preparations of curare.

KAY.

Crutcher, R. R., and Daniel, R. A., Jr.: Pulmonary Embolism, A Correlation of Clinical and Autopsy Studies. Surgery 23:47 (Jan.), 1948.

There have been 83,984 admissions to the Vanderbilt University Hospital between 1930 and 1944, inclusive. Four thousand one hundred eighty-two patients (excluding still births) died in the hospital and 2,580 (63 per cent) came to autopsy. There were 35,540 operations (including ear, eye, nose, and throat) carried out during this fifteen-year period. Fifty-five patients had fatal pulmonary emboli, confirmed by autopsy, twenty-five occurring postoperatively. On the basis of 100 per cent autopsies there would have been an expected incidence of thirty-nine cases. Hence, the incidence of fatal pulmonary emboli occurring postoperatively is 0.109 per cent or one in 911 operations.

The authors point out that the incidence of fatal pulmonary emboli is greater in seriously ill patients than in patients who are relatively good risks and whose surgical condition carries a favorable prognosis. In twenty-three of fifty-five autopsy records, thrombi were found in the veins of the pelvis and upper abdomen. There were three cases in which the origin of the emboli was the right side of the heart.

It is pointed out that restriction of activity or fixation of patients in bed is more important than early ambulation as a means of preventing pulmonary emboli. There were 2,107 admissions for pulmonary tuberculosis during this period and although the majority of these patients were confined to bed they were permitted to move about in bed without restriction. There was no instance of fatal pulmonary embolism in this group.

LORD.

Singleton, A. O., and Singleton, A. O., Jr.: Cerebral Hemorrhage Following Repair of A Common Carotid-Internal Jugular Arteriovenous Fistula. Surgery 23:75 (Jan.), 1948.

The authors discuss fifty cases in the literature of common carotid-internal jugular fistulas, pointing out that seventeen of the patients had restoration of arterial flow while the remaining thirty-three had interruption of the flow by ligation of the common carotid artery. It is of significance that in the group of seventeen patients in whom arterial flow was restored there was only one death, and this was the result of bronchopneumonia. In the group of thirty-three who had arterial interruption, there were three deaths and three recurrences, two deaths having been due to cerebral anemia and one, to coronary occlusion. In addition, one patient had a hemiplegia following ligation of the carotid artery.

The authors report an instance of an arteriovenous fistula between the common carotid artery and internal jugular vein treated by maintainance of arterial continuity and followed by cerebral hemorrhage and death. The patient, a 49-year-old farmer, had been struck in the neck by a rock at the age of 12 years and shortly thereafter had noticed a whirling sound in the head. Three years before his admission, a swelling had appeared in the left side of the neck and for three months the patient had experienced exertional dyspnea and palpatation. Physical examination

revealed the typical signs of an arteriovenous fistula in the left side of the neck and great enlargement of the heart. The operation was carried out under local and cyclopropane anesthesia. The opening in the artery was sutured transvenously and the vein was doubly ligated with excision of the fistula. The patient was returned to the ward in good condition, but four hours postoperatively he could not be aroused and died within one hour. Autopsy revealed the artery in the neck to be intact and there was no evidence of a thrombus. A large hemorrhage had occurred from the left ventriculostriate artery with a large intracerebral blood clot 6 cm. in diameter. In discussion the authors point out that with closure of the fistula the pressure in the carotid artery rose greatly and probably was the cause of the rupture of the intracranial artery.

LORD.

Light, F. P.: A Nine-year Follow-up in Cases of Toxemia of Pregnancy. Am. J. Obst. & Gynec. 55:321 (Feb.), 1948.

This study is based on a review of the records of 391 women of a total of 530 toxemia clinic patients. Of the 391, thirteen had eclampsia, 275 had mild pre-eclampsia, and 103 had severe pre-eclampsia. The most common residual damage is hypertension. In only a few cases has there been shown to be any renal damage. The study indicated that the duration of the toxemia had little bearing upon the incidence of residual damage. Age, however, is a more important factor. The incidence of residual damage progressively increases with the age of the patient. Among the 103 patients with severe pre-eclampsia, residual damage occurred in forty four (42.5 per cent), whereas residual damage occurred in only seventy (25.4 per cent) of 275 patients with mild pre-eclampsia. The author seriously questions the validity of the assumption that hypertension occurring after toxemia is due to residual damage, but rather feels that it is coincidental essential hypertension manifesting itself.

WAGNER.

Maeck, J. Van S., and Zilliacus, H.: Heparin in the Treatment of Toxemia of Pregnacy. Am. J. Obst. & Gynec. 55:326 (Feb.), 1948.

In general, the pathologic changes found in women who die from toxemia of pregnancy consist of capillary or arteriolar lesions in different organs, with scattered thrombi in these vessels. Isoagglutination reactions are frequently reported in pregnant patients. Heparin is known to inhibit to some degree the isoagglutination of red blood cells.

A case of pre-eclampsia near term characterized by blurred vision, headache, some edema, and a blood pressure of 170/110 was treated by the continuous intravenous infusion of 150 mg. of heparin in distilled water and 5 per cent dextrose over a period of four and one-half hours. The clotting time rose to eighteen minutes. Following this treatment, the patient showed subjective and objective improvement. Within twenty four hours albuminuria was reduced to a faint trace and the blood pressure, to 140/84. The patient delivered normally thirteen days later.

WAGNER.

Crocket, K. A., and Rhoads, P. S.: Hyperthermia Caused by Penicillin-Heparin in the Treatment of Subacute Bacterial Endocarditis. Ann. Int. Med. 28:456 (Feb), 1948.

Prolonged hyperthermia of alarming degree accompanied the use of large amounts of penicillin with minimal amounts of heparin in the treatment of a patient with subacute bacterial endocarditis who ultimately recovered as a result of such treatment. The evidence seemed to point toward heparin as the cause of the hyperthermia. This type of unusual reaction to heparin must be remembered since it can make it difficult to determine whether the prolonged fever in a patient with subacute bacterial endocarditis is the result of the disease process or the result of the medication.

WENDKOS.

Prinzmetal, M., Simkin, B., Bergman, H. C., and Kruger, H. E.: Studies on the Collateral Circulation of the Normal Human Heart by Coronary Perfusion With Radioactive Erythrocytes and Glass Spheres. Arch. Inst. de Cardiol. de Mexico 18:122 (Feb. 20), 1948.

The authors present two new methods for the study of the collateral circulation of the human heart in post-mortem experiments. The first method was based on perfusion by means of red

cells labeled with radioactive phosphorus in suspension in saline solution. Small quantities of radioactive cells can easily be measured by means of Geiger counters or by exposure of the heart to x-ray films for many hours. The second method consisted of the injection of glass spheres of known size through one of the coronary arteries. The spheres were collected at the opposite coronary artery, the coronary sinus, and the ventricular cavities. The diameters of the various anastomoses were thus measured.

After perfusion of one of the branches of the left coronary artery, large amounts of labeled red cells were found in both ventricles. This indicated the existence of numerous anastomoses between the ventricles.

The largest intercoronary anastomoses permitted the passage of spheres of 180 micra and were, therefore, in the arteriolar range. The anastomotic channels between the coronary arteries and either of the ventricular cavities ranged from 70 to 350 micra. They represented arterioluminal and arteriosinusoidal vessels, or Thebesian veins.

The authors conclude that the normal human heart has an extensive collateral circulation with various types of anastomoses. This collateral circulation may function in case of emergency and may enlarge if the pressure gradient is favorable. The evidence shows that collateral circulation does function, in a limited manner, after an acute coronary occlusion. It is not sufficient to prevent an infarct following obstruction of a major coronary artery, but it may limit the size of the infarction.

LUISADA.

Alstad, K. S.: Effect of Thiocyanate on Basal Blood Pressure. Brit. Med. J. 1: 250 (Feb. 7), 1948.

The author states that many are not convinced of the satisfactory effect of thiocyanates in the treatment of hypertensive disease and refers to a paper by Foster (1943) in which it is stated that there is no evidence of hypotensive effect of thiocyanates in animals, short of a toxic dose.

The author uses (1) casual, (2) basal, and (3) supplemental blood pressures as a means of study and observation. Casual pressure is that recorded after a few minutes' rest in recumbency. Basal pressure refers to pressure recorded when the patient is in a state of basal metabolism (after a night's rest, habituated to surroundings, and so forth). The supplemental pressure refers to the difference between these readings and records the influence of the physical, emotional, and metabolic factors. The author feels that the basal pressure is rather constant in hypertensive patients.

In twenty patients investigated so far, the preliminary investigations indicate that thiocyanates cause a fall in the basal and supplemental pressure compared with the effect of placebos.

The author describes a case demonstrating his point of view. The initial casual pressure at the time of admission for hypertensive encephalopathy was 190/110. The basal pressure next morning was 128/84. At the end of seventeen weeks of therapy the casual pressure was 125/84 and the basal pressure, 88/52. The drug was withdrawn because of diarrhea, which was considered to be toxic, and the blood pressure again rose to initial levels, only to return to optimal levels on administration of the drug again.

The author concludes that a well-marked fall in blood pressure occurs in some patients with essential hypertension following treatment with thiocyanates.

WAGNER.

Schoenewald, G.: Treatment of Angina Pectoris by Reduction of Basal Metabolism. Brit. M. J. 1: 251 (Feb. 7), 1948.

"From the therapeutic point of view sufferers with angina can be divided into obese, anemic or slim types." The author states that the first two groups are amenable to treatment by reduction of weight and correction of anemia. The third type can be given nitroglycerin either to shorten the attacks or occasionally to prevent them. In connection with the slim type of patient having angina, total thyroidectomy in order to "shed the load" from a failing heart was done with some success fifteen years ago. Today, thiouracil and its derivatives make such major surgery unnecessary.

Three patients with angina pectoris and positive electrocardiographic signs were treated with methylthiouracil. No effort was made to check the basal metabolic rates, as this was considered unnecessary. Their case histories are reported. Relatively large doses (0.6 Gm.) for five to six weeks or more were required before myxedema or relief from angina occurred.

WAGNER.

McKeown, F.: **Acute Rheumatism in Pregnancy.** J. Obst. & Gynaec. Brit. Emp. 60: 50, (Feb.), 1948.

"The main purpose of this paper is to report two cases of pregnancy complicated by acute rheumatic heart disease." There was no clinical evidence of the condition in these patients, while the heart showed severe myocardial damage. Brief summaries of the clinical records and of the pathologic reports are given. In short, the patients were well throughout pregnancy, but collapsed and died following delivery. The heart in each instance showed acute rheumatic endocarditis and myocarditis. In retrospect, the hearts of six pregnant patients with mitral stenosis who died from cardiac failure were re-examined and four showed evidence of recent rheumatic myocardial lesions. The author comments as follows: (1) Even in a heart not the site of a mechanical lesion, recurrent rheumatic carditis may be responsible for acute myocardial failure; (2) it is dangerous to correlate the presence of a chronic valvular lesion with fatal outcome in the absence of microscopic examination of the heart.

WAGNER.

Gruhzit, O. M., Fisken, R. A., and Cooper, B. J.: Tetraethylammonium Chloride ($N(C_2H_5)_4NCl$). Acute and Chronic Toxicity in Experimental Animals. J. Pharmacol. & Exper. Therap. 92:103 (Feb.), 1948.

Tetraethylammonium chloride was administered both orally and parenterally in albino mice, albino rats, and dogs. With large doses, no matter what the route of administration, the animals died within ten to thirty minutes of respiratory failure. The following signs occurred before death: "Severe incoordination, flaccid prostration, respiratory and cardiac depression, marked ptosis and edema of eyelids, mydriasis, ocular muscle paralysis (inversion of eyeballs), erythema of ocular, nasal, and less so of buccal membranes, paralysis of accessory respiratory muscles of chest, and death from respiratory and circulatory collapse."

Sublethal doses were well tolerated when given over long periods of time, even when the amount of drug given was large enough to cause some of these signs two to three hours after administration. During chronic toxicity experiments with sublethal doses, there were no hematologic, renal, or hepatic signs of damage that could be detected by blood counts, total blood nonprotein nitrogen, total plasma protein, albumin-globulin fractions, bromsulphalein blood concentration, or urinalysis.

Necropsy lesions in acute toxicity experiments consisted in "severe congestive blood stasis and petechial hemorrhages in visceral organs, liver, lungs, kidneys, spleen, gastrointestinal tract, urinary bladder, and brain." Edema and necrotic changes were noted around the central veins of the liver. Cloudy swelling was noted in the kidneys, along with changes in the cytoplasm of the cells lining the loops of Henle.

Repeated administration of sublethal doses produced no significant pathologic lesions.

GODFREY.

Lipschitz, W. L., and Stokey, E.: Diuretic Action of Formoguanamine in Normal Persons. J. Pharmacol. & Exper. Therap. 92:131 (Feb.), 1948.

The authors have previously reported the mode of diuretic action of formoguanamine (J. Pharmacol. & Exper. Therap. 83:235, 1945).

Formoguanamine has been found to be markedly more effective as a diuretic than urea. Studies on dogs and rabbits failed to reveal any significant toxicity.

Eight healthy male volunteers were given formoguanamine in doses from 3.5 to 11.0 mg. per kilogram of body weight. It was found to give a more consistant diuresis than either caffeine

or theobromine. Both sodium chloride and water excretion were increased. No toxicity was noted among the eight volunteers.

GODFREY.

McNamara, B., Krop, S., and McKay, E. A.: The Effect of Calcium on the Cardiovascular Stimulation Produced by Acetylcholine. J. Pharmacol. & Exper. Therap. 92:153 (Feb.), 1948.

Acetylcholine causes a pressor response in animals that have been atropinized. This response, in turn, may be blocked by nicotine. The pressor response caused by acetylcholine was believed to be due to ganglionic stimulation; its blockage by nicotine was believed to be due to ganglionic blockage.

The authors showed that by administering calcium they were able to inhibit the ganglionic blocking action of nicotine so that the acetylcholine effect was not abolished. This could be demonstrated both on the intact animal and on the isolated heart. They also demonstrated that calcium potentiates the epinephrine effect upon the heart. They believe that acetylcholine acts directly upon the cardiac musculature by liberating an epinephrine-like substance. The fact that calcium potentiates epinephrine effects and also overcomes nicotine blockage sheds further light on its cardiac effects and the mechanism by which it acts upon the heart.

GODFREY.

Brown, H. S., Allen, E. V., and Craig, W. McK.: The Effect of Tetra-ethyl-ammonium Choloride on Blood Pressure Before and After Sympathectomy for Hypertension. Proc. Staff Meet., Mayo Clin. 23:94 (Feb. 18), 1948.

Nine subjects who failed to obtain an entirely satisfactory reduction of the blood pressure from transdiaphragmatic or infradiaphragmatic sympathectomy were investigated. When tetraethylammonium chloride was given intravenously after postoperative periods of from two weeks to four years, the blood pressure of eight of the nine subjects was temporarily reduced to normal. In the ninth case, exceptional because of nephrectomy as well as sympathectomy, the blood pressure actually increased following the injection. The blood pressure of only one of six patients tested preoperatively was reduced to normal.

The authors feel that these observations suggest that hypertension which persists after sympathectomy is not due to organic changes which affect the lability of the arterioles. They explain the difference in the blood pressure response after sympathectomy as being the result either of an increased susceptibility of the arterioles to the drug or of a more complete block of the remaining ganglia by the drug following sympathectomy. These observations may be a clue to the genesis and treatment of hypertension.

ARKLESS.

Wegria, R., and Boyle, M. N.: Correlation Between the Effect of Quinidine Sulfate on the Heart and Its Concentration in the Blood Plasma. Am. J. Med. 4:373 (March), 1948.

The authors have attempted to correlate the concentration of quinidine in the plasma and in the heart and the intensity of the effect of quinidine on the heart.

The first part of the experiment consisted of ten studies on six patients to correlate the plasma concentration of quinidine and the intensity of the effect of quinidine on the heart as measured by the changes of the rate of the circus movement in auricular fibrillation. Single and/or repeated oral doses of quinidine sulfate were given patients with chronic auricular fibrillation. The intensity of cardiac effect of the drug and its plasma concentration were found to be grossly parallel, but not parallel in a strictly quantitative manner. Discrepancies were found in that the plasma level of the drug decreased faster than the intensity of its cardiac effect.

The second part of the experiment involved the determination of the concentration of quinidine in the plasma and heart muscle of dogs given the drug orally. These experiments showed that the concentration of quinidine in the tissues is much higher then the plasma concentration. The peaks of tissue and plasma concentration correspond as far as time is concerned.

The authors believe that if the results of the experiments performed on dogs are applicable to man, the main factor accounting for the discrepancies between quinidine plasma concentration and intensity of the effect on the heart is the fact that the cardiac effect is not proportional either to the plasma or to myocardial concentration of the drug. It would appear that a further increase in the heart concentration yields a diminished increment of cardiac effect.

WOODS.

Grayson, C. E.: Cardiac Calcifications, Annular and Valvular (Leaflet). California Med. 68:121 (March), 1948.

A brief discussion of calcareous deposits in the aortic and mitral annulus and in the valve leaflets is presented. The average age of women with calcifications is consistently greater than that of men except in the group with calcifications of the aortic ring. The average age of patients having ring calcifications is greater than the age of those having leaflet calcifications. If the group with both aortic ring and mitral ring calcifications is combined with the group having isolated calcifications of the aortic ring, the average age difference becomes still greater. The average age of patients having mitral leaflet calcifications is considerably lower than the average age of those with calcifications in the mitral annulus.

The incidence of hypertension is higher in those patients having mitral or aortic and mitral ring calcifications. The association of other visible calcifications in the arteries and in the bronchi is also higher in these groups. The lack of abnormal electrocardiographic findings in patients with aortic calcifications of slight or moderate degree and in patients with mitral ring calcifications is consistent with the lack of effect of these lesions upon the heart function. The incidence of a rheumatic fever history is considerably higher in those with leaflet calcifications.

Aortic ring calcifications may occur in association with heart disease or it may be incidental to other visceral disease. Calcifications in the mitral annulus fibrosus are probably of less clinical importance than calcification in the aortic ring. Mitral annulus deposits can be entirely unsuspected until the patient is fluoroscoped. Small mitral leaflet calcifications are distinguished from calcifications of the ring by their snapping motion and by the more localized extent of the deposit.

It seems clear that the deposits of calcium are due to more than one disease process. The annular type occurs in older people and is probably related to an atherosclerotic process. The leaflet type occurs in younger people and is probably related to rheumatic heart disease. Since fluoroscopy permits distinction between annular and leaflet calcification, one has an additional aid in distinguishing rheumatic from nonrheumatic heart disease.

BELLET.

Kempner, W.: Treatment of Hypertensive Vascular Disease With Rice Diet. Am. J. Med. 4:545 (April), 1948.

The article is one of a series of seminars on hypertension and summarizes the author's experience with the use of the rice diet in 500 patients with hypertensive vascular disease. It is stated that the diet has been ineffective in 178 patients while it proved beneficial in 322 as judged by production of one or more of the following effects: decrease in "mean" arterial blood pressure of at least 20 mm. Hg; reduction in heart size with change in the transverse diameter of 18 per cent or more; a change in T_1 of the electrocardiogram from completely inverted to upright; and disappearance of severe retinopathy. Subjective improvement has not been accepted as evidence of successful therapy. Whether the effect of the diet is due to its low sodium content, low cholesterol content, or other factors is as yet unsettled.

The regimen is described in detail, and indications and contraindications are given. Data are presented to show that protein equilibrium, hemoglobin, and plasma proteins are maintained, while hypercholesterolemia decreases markedly on the diet. There is a decrease of sodium and chloride concentration in urine and serum and a decrease in excretion of chloride, sulfate, and ammonia in the urine.

WOODS.

Ross, R. A., Lambeth, S. S., Thomas, W. L., and Carter, F. B.: Fifty-Four Deaths Occurring in Pregnant Patients Who Had Hypertension. Am. J. Obst. & Gynec. 55:591 (April), 1948.

The material consisted of fifty-four patients who died in the immediate puerperium or in pregnancy and who had a blood pressure higher than 140/90. There were only seventeen living children from the fifty-four dead mothers. An elevated diastolic pressure was the common denominator of all patients. Many of the patients were colored, and previous histories regarding hypertension were unknown in twenty-five of the fifty-four cases. Most of the patients were over 30 years of age. The average number of previous pregnancies was 5.8; the average number of living children was 4.6. Changes in the optic fundi, such as thinning of vessels, increased light reflex, tortuosity, and a-v nicking, were present in thirty-eight cases. A total of twenty-five patients were thought to have enlarged hearts, and thirty-three of forty-six patients were overweight.

The authors conclude that the hypertensive woman with enlarged heart, changes in optic fundi, and albuminuria has a poor prognosis when pregnant. Serious consideration of interruption by the most conservative means should be given such patients, regardless of the stage of pregnancy, and contraceptive measures should be suggested.

WAGNER.

Blumgart, H. L., and Altschule, M. D.: Clinical Significance of Cardiac and Respiratory Adjustments in Chronic Anemia. Blood 3:329 (April), 1948.

The status of the cardiorespiratory system and the related manifold compensatory mechanisms which provide a maximal supply of oxygen to the tissues in the presence of anemia are discussed.

In chronic anemia, when the oxygen-carrying capacity of the blood is diminished, an adequate supply to the tissues is maintained by an increased cardiac output, an increased velocity of blood flow, and a relatively more complete abstraction of oxygen from the blood as it passes through the capillaries. Related to the increased blood flow is a decrease in peripheral resistance, but it is not uniform, resulting at times in a reduced blood flow in the hands and feet while the blood flow of other parts of the body is increased. The metabolic rate is not strikingly altered. The blood volume is generally slightly reduced but the plasma volume is normal. The deviations from the normal values vary from patient to patient, but generally are definite when the hemoglobin values are less than 50 per cent and are greatest at the lowest levels of hemoglobin concentration.

Changes in respiration favor the occurrence of exertional dyspnea. These changes are: an increased respiratory minute volume, a decreased vital capacity including the reserve and complemental air volumes and an increased residual air. Abnormalities in carbon dioxide transport and dissociation, reduced arterial oxygen capacity, and decreased blood oxygen saturation during effort, together with the frequently observed elevated blood lactic acid values, are noted.

The clinical manifestations of chronic anemia include cardiovascular and respiratory symptoms and signs. The cardiac manifestations include palpitation and dyspnea on exertion, tachycardia, cardiac enlargement, murmurs, and electrocardiographic changes. It is observed that the arterial blood pressure is frequently lowered while the venous pressure is generally within the limits of normal. The occurrence of angina pectoris and congestive failure in some patients with the development of anemia, and their disappearance as the anemia is alleviated, is discussed.

The problem of differentiating the concomitant occurrence of exertional dyspnea, edema, and hepatomegaly in severe anemia from their occurrence in myocardial insufficiency presents itself. Aid is derived from the absence of venous engorgement and orthopnea in anemia; the absence of cyanosis cannot be relied upon since cyanosis cannot occur if the patient has less than 5 grams per cent of hemoglobin.

BEIZER.

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CONFERENCE OF LOCAL HEART ASSOCIATIONS DISCUSSES COMMUNITY PROGRAMS AND COOPERATION IN 1949 NATIONAL CAMPAIGN

Presidents and chairmen of the governing boards of affiliated local heart associations and representatives from many states and cities interested in forming new local heart associations attended a special conference at the Hotel Plaza, New York, on September 24, under the auspices of the American Heart Association. The purpose of the conference was to discuss plans for the development of new community programs to combat heart disease through the creation of additional heart associations as well as the strengthening of existing associations.

A preview of plans for the Association's 1949 national educational and fund-raising campaign was presented to the conference along with suggestions for local participation. It was announced that Harold Stassen had accepted the post of National Campaign Chairman, heading a National Campaign Planning Committee composed of such prominent figures as Winthrop Aldrich, Chairman, Chase National Bank of the City of New York, who will serve as Campaign Treasurer; Colby M. Chester, Honorary Chairman of General Foods Corporation; Henry R. Luce, Publisher, Time Magazine; Charles E. Wilson, President, General Motors Corporation; and Mark Woods, President, American Broadcasting Company.

Under the chairmanship of Thomas I. Parkinson, President, Equitable Life Assurance Society, an even more extensive list of prominent Americans comprising the National Sponsors Committee for the forthcoming campaign was announced. These include Albert B. Chandler, Baseball Commissioner; Dr. James B. Conant, President, Harvard University; Gardner Cowles, President and Editor, Look Magazine; Walter S. Gifford, Chairman, American Telephone and Telegraph Company; Tom M. Girdler, Chairman, Republic Steel Corporation; William Green, President, American Federation of Labor; Phillip Murray, President, Congress of Industrial Organizations; Herbert H. Lehman, former Governor of New York; Elmo Roper; Niles Trammel, President, National Broadcasting System; and Owen D. Young, Honorary Chairman, General Electric Company.

A. W. Robertson, Chairman of the Board of the Association, emphasized the need for new local affiliates to direct and coordinate community services for cardiac patients so that the latest advances of medical research may be brought swiftly to the individual in his own community. Dr. Charles A. R. Connor, Medical Director of the Association, introduced to the conference delegates the newly published "Program Guide for Local Heart Associations." He explained that the purpose of the booklet, which has been distributed to all affiliates of the Association, is to present a broad framework for local programs adaptable to meet specific community needs. Dr. Connor said the Association hoped eventually to have an enlarged field staff to assist in the organization of local affiliates and in the development of local programs.

Dr. Connor announced that the recently organized National Conference of Executive Secretaries of local heart associations would meet in New York on October 19 and 20. The purpose of this group is to serve in an advisory capacity concerning the needs and requirements of local affiliates and the implementation of American Heart Association policies with reference to community programs.

Dr. T. Duckett Jones, Member of the Board of Directors of the Association, reviewed the recently published booklet outlining policies adopted by the Assembly last June. Dr. Jones emphasized the need for a strong national organization to assist in the development of community programs. He pointed out that the policies of the Association were designed to aid in the

organization of additional cardiac services and facilities throughout the entire country, the planning of preventive measures, the application of scientific knowledge, and the correlation of existing agencies. Dr. Jones urged local associations to develop a carefully planned and integrated program, with emphasis on improved service to the individual. Such a program, he said, may require many years to develop, but it should encompass the entire field of cardiovascular disease and should be adapted to the needs of various areas.

Dr. H. M. Marvin, President-Elect of the Association, summarized the "Recommendations From the Research Policy Committee" which state that "the ultimate aim is to develop a continuing program of productive research . . . over the country as a whole, rather than in a few centers only." The recommended program will include the training and support of career investigators in the field of cardiovascular disease, research fellowships, and the provision of grants for approved research projects. To develop the program, a Research Allocations Committee is to be elected by the Scientific Council of the Association.

Dr. G. K. Fenn acted as Chairman at the morning session, while Mr. Robertson presided over the afternoon session, which concentrated on fund-raising and promotional plans for the 1949 National Campaign.

E. J. Ade, the Association's Fund-Raising Director, outlined campaign organizational procedures and methods of fund-raising. Mr. Ade explained that a goal of $5,000,000 had been decided upon for the 1949 campaign on the basis of a study of what the Association, in its present state of development, could accomplish with that amount. Discussing the services which the National Campaign Headquarters would render for local cooperating groups and affiliated associations, Mr. Ade mentioned leadership and guidance in campaign planning, fund-raising assistance, and a national publicity and educational program.

Mr. Ade exhibited the Plastic Heart coin bank which will again be available as a fund-raising device, and a new "Save-a-Heart" bank for smaller contributions. He said that a Campaign Chairman's Handbook, containing specific suggestions for local organization and promotion, will be distributed shortly.

M. Frederick Arkus, of Win Nathanson Associates, public relations counsel for the Association, presented the basic public relations objectives of the forthcoming campaign. These include education of the public about the problem of heart disease and the accomplishments of science, identification of the Association in the public consciousness in order to win acceptance and support, and laying of the groundwork for the development of local heart associations and community programs. Mr. Arkus outlined plans for the national publicity program, which will support local efforts, through all media of information, including national wire services, syndicates, magazines, radio, television, and motion pictures. He also illustrated the type of campaign posters and educational pamphlets which will be distributed to local groups.

Among those attending the conference were representatives from Chicago, New York, Philadelphia, St. Louis, Kansas City, New England, Ohio, New Jersey, Florida, Texas, Louisiana, Wisconsin, Minnesota, and Maryland.

As the American Heart Journal went to press, the National Campaign Planning Committee and the National Sponsors Committee were still in the process of formation. The following are the names of those who had already accepted membership on these campaign committees:

MEMBERS OF NATIONAL CAMPAIGN PLANNING COMMITTEE

Name	Title	Company	City
Winthrop W. Aldrich	Chairman	Chase National Bank of the City of New York	New York
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MEMBERS OF NATIONAL CAMPAIGN PLANNING COMMITTEE—Continued

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MEMBERS OF NATIONAL SPONSORS COMMITTEE

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Thomas I. Parkinson	President	Equitable Life Assurance Society	New York
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Original Communications

REPORT OF THE COMMITTEE FOR THE EVALUATION OF ANTI-COAGULANTS IN THE TREATMENT OF CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION

(A Progress Report on the Statistical Analysis of the First 800 Cases Studied by This Committee)

Irving S. Wright, M.D., Charles D. Marple, M.D., and Dorothy Fahs Beck, Ph.D.
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The possibility of preventing the extension of coronary thromboses and the development of mural thrombi in the presence of myocardial infarction by the use of anticoagulants was suggested by Solandt, Nassim, and Best[1,2] in 1938. These investigators were able to prevent the development of both coronary thrombi and of intracardiac mural thrombi, under conditions in which such thrombi are usually produced experimentally in animals, by the use of the anticoagulant, heparin. Their observations were not applied to man on any significant scale because of the difficulties and the risk felt to be inherent in the use of heparin clinically. In the years 1945 and 1946, Wright,[3] Nichol and Page,[4] and Peters, Guyther, and Brambel[5] reported encouraging results following the use of the anticoagulant, Dicumarol, in the treatment of coronary thrombosis with myocardial infarction in man. These reports were preliminary in nature since only small numbers of cases were studied. However, the uniformly favorable results appeared to justify a more extensive study of the use of anticoagulants in the treatment of coronary thrombosis.

The findings of this Committee, the result of a joint research project sponsored by the American Heart Association, are being presented jointly by the American Heart Journal and the Journal of the American Medical Association.

This study has been supported by grants from the United States Public Health Service.

Presented at the Twenty-first Annual Scientific Meeting of the American Heart Association, Chicago, Ill., June 18 and 19, 1948.

Accordingly, in the spring of 1946, the Board of Directors of the American Heart Association authorized the formation of the Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis With Myocardial Infarction. This committee is composed of internists with special interest in cardiovascular diseases who are associated with the sixteen hospitals which have contributed cases to this study. Workers in several additional institutions have participated in an advisory or consulting capacity. The participating hospitals and the responsible investigators are as follows:

Participating Hospitals

Bellevue Hospital, New York	John E. Deitrick, M.D.
Beth Israel Hospital, Boston	Herrman L. Blumgart, M.D.
Bronx Veterans Hospital	Louis A. Kapp, M.D.
Cincinnati General Hospital	Johnson McGuire, M.D. Helen Glueck, M.D.
Cleveland City Hospital	Roy W. Scott, M.D.
Henry Ford Hospital, Detroit	F. Janney Smith, M.D.
Jackson Memorial Hospital, Miami	E. Sterling Nichol, M.D.
Lakeside Hospital, Cleveland	Joseph Hayman, Jr., M.D. Harold Feil, M.D.
Massachusetts General Hospital	Howard B. Sprague, M.D.
Michael Reese Hospital, Chicago	Louis N. Katz, M.D.
Mount Zion Hospital, San Francisco	John J. Sampson, M.D.
Pennsylvania Hospital, Philadelphia	Joseph B. Vander Veer, M.D.
Peter Bent Brigham Hospital	Samuel A. Levine, M.D.
Rhode Island Hospital, Providence	Frank B. Cutts, M.D.
San Francisco County Hospital	John J. Sampson, M.D.
The New York Hospital	Irving S. Wright, M.D. Harold J. Stewart, M.D.

Consultants

Ralph S. Overman, Ph.D.
Charles E. Brambel, Ph. D.
Nelson W. Barker, M.D.
Grace Goldsmith, M.D.
Marjorie Bellows, Ph.D.

Central Laboratory

Irving S. Wright, M.D., Chairman of Study
Charles D. Marple, M.D., Coordinator
Dorothy F. Beck, Ph.D., Statistician

Each investigator has been assisted by a team of residents, fellows, and associates from his staff. Full credit must be accorded each of these workers whose whole-hearted cooperation has been indispensable to the success of this study. It is a pleasure to report that 1,000 patients with coronary occlusion and myocardial infarction have been studied under the conditions of this investigation.

PLAN OF THE STUDY

Slightly fewer than one-half of these 1,000 patients have been treated by conventional methods of therapy alone. The others have been treated with anti-

coagulants, in addition to conventional methods. A record of each case has been prepared in detail on master forms by the responsible investigator and his associates and forwarded to the Central Office of the Committee at The New York Hospital. The master forms are being subjected to intensive statistical analysis and a definitive report on the 1,000 cases will be prepared as promptly as the analysis will permit. The present report includes data obtained from analysis of the first 800 cases reported to the Central Laboratory. Although it is possible that the addition of the last 200 cases, and other later revisions, may change the figures somewhat, it is unlikely that the conclusions will be altered significantly since the relationship of the control and treated groups as to deaths and thromboembolic complications has remained relatively stable as the sample has increased in size.

Three hundred sixty-eight patients admitted to the participating services on *even* days received conventional therapy and constitute "the control group." Four hundred thirty-two patients admitted on *odd* days received anticoagulants in addition to conventional therapy and constitute "the treated group."

The principles used as guides in the administration of Dicumarol and heparin were as follows:

a. Heparin may be given for the first forty-eight hours or more, if desired.

b. Prothrombin determinations are to be done each day and no Dicumarol should ever be ordered unless the morning prothrombin report is available.

c. Dicumarol, 200 to 300 mg. daily, should be given until the prothrombin time is 30 seconds.

d. Dicumarol, 50 to 100 mg. daily, should be given if the prothrombin time is between 30 and 35 seconds.

e. Dicumarol is withheld if the prothrombin time is 35 seconds or more. Then, no drug is given until the prothrombin time is again down to 30 seconds or less, after which the drug is again given cautiously in 100 mg. doses.

f. The Link-Shapiro technique, using undiluted whole plasma, or the Quick method is to be used for determining the prothrombin clotting time and it is suggested that the Link-Shapiro method, using 12.5 per cent diluted plasma, be employed as an additional check or safeguard. All prothrombin times are given in terms of the Link-Shapiro (undiluted) method.

g. Unless contraindications arise, the Dicumarol therapy is to be continued in the chosen cases over a minimum period of thirty days; preferably thirty days after the last thromboembolic episode.

h. In instances of hemorrhagic manifestations, the use of synthetic vitamin K preparations in doses of 60 to 75 mg. and transfusions of fresh whole blood (may be citrated) are recommended.*

A comparison of the patients in the "control" group with those in the "treated" group shows a striking similarity with regard to age, history of previous infarction, and estimated severity of the present attack, as shown in Table I. The average age of the control group was 60 years; that of the treated group, 59 years. The average age of men in the control group was 58.9 years, and in the treated group, 57.2 years. The average age of women in the control group was

*From the instructions issued to each participating team (slightly modified).

64.1 years, and in the treated group, 64.6 years. In this series of 800 cases, the average age of female patients was approximately 6.4 years greater than that of male patients.

TABLE I. COMPOSITION OF SAMPLE. TOTAL GROUP: 800 CASES OF CORONARY OCCLUSION WITH MYOCARDIAL INFARCTION SURVIVING FIRST DAY OF HOSPITALIZATION

ITEM COMPARED	CONTROL GROUP (EVEN DAYS)	TREATED GROUP (ODD DAYS)
Number of cases	368	432
Average age	60 years	59 years
Proportion males	77%	76%
One or more previous infarctions	24%	22%
Illness "severe" at onset	23%	30%
Anticoagulant therapy received (exceptions as noted)	88% no anticoagulants 12% some anticoagulants (primarily after complications)	81% Dicumarol without heparin 14% Dicumarol plus some heparin 3% no anticoagulants because of renal or liver disease or hemorrhage 2% no anticoagulants because of miscellaneous errors

Analyzing the two groups for a history of one or more previous myocardial infarctions, it was found that 24 per cent of the control group and 22 per cent of the treated group had had one or more previous infarctions.

An estimate of the severity of the attack was made for each patient at the time of diagnosis and recorded as mild, moderate, or severe. Twenty-three per cent of the control group and 30 per cent of the treated group were classified as having severe attacks. Although this classification is admittedly arbitrary, the results suggest that the treated group contains a somewhat greater proportion of severely ill patients. The control and treated groups were also closely similar when the medical histories of cardiovascular diseases and the locations of their original infarcts were compared.

Eight-eight per cent of patients in the control group received no anticoagulant, but 12 per cent did receive some anticoagulant therapy, often for short periods only. Anticoagulants were administered to patients in the control group following the development of a thromboembolic complication because of pressure on the part of the family or a private physician* or for miscellaneous reasons. Of the treated group, 81 per cent received Dicumarol only, while 14 per cent received Dicumarol and some heparin. In three per cent of the "treated cases" no anticoagulants were given because of concurrent renal or hepatic disease or because of hemorrhagic conditions, and 2 per cent received no anticoagulant because of miscellaneous errors.

In the computation of the rates of incidence upon which all of the following charts are based, small and conservative corrections were made in order to simplify

*This factor became intensified as the study progressed.

the presentation. In the control group the rates are corrected for exceptions to the "no anticoagulant" rule. Rates as shown are those it is estimated would have occurred if no patient in the control group had received any anticoagulant. They differ only slightly from the data as actually reported and are believed to present a truer picture of rates without anticoagulants. In the treated group the rates are corrected for erroneous omissions of anticoagulants. There is evidence that with more intensive and inclusive anticoagulant therapy, the rates for death and complications in the treated group would have been lower than those shown. No correction was made for those patients from whom anticoagulants were withheld because of specific contraindications. These omissions are considered to be disadvantages inherent to this type of therapy.* In both groups all rates for thromboembolic complications and hemorrhagic manifestations, as stated in this interim report, refer to conditions diagnosed clinically. Statistics based on autopsy findings are not yet available, but are being analyzed at this time.

RESULTS

Fig. 1 illustrates the contrast between the death rates in the control group and in the group who received anticoagulant therapy. Twenty-four per cent of the control patients died, whereas 15 per cent of the treated patients died. Thus, somewhat more than one-third of the individuals who would have died without anticoagulant therapy survived the specific attack under consideration when anticoagulants were given. This difference is statistically significant.† Further examination indicates that the greatest improvement was achieved in patients who had suffered one or more thromboembolic complications prior to death. Such deaths occurred in roughly 10 per cent of the control cases, but in only 3 per cent of the treated cases. Death, not preceded by a clinically recognized thromboembolic complication, occurred in approximately 14 per cent in the control group as against 12 per cent in the treated group. As previously anticipated, anticoagulants reduced the death rate largely by reducing the incidence of those thromboembolic complications which, directly or indirectly, result in death.

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*These corrections were made by it being assumed that if anticoagulants had been completely withheld from all control patients receiving anticoagulants, they would have developed at least as many further complications and would have died at least at the same rate as did control patients of comparable age who received no anticoagulants at any time under approximately comparable circumstances. If actual rates for subgroups among these patients for whom exceptions were made did not already exceed these estimates, the estimates were substituted for the actual data for these particular subgroups. An appropriate modification of this correction procedure was applied in the case of the treated group and for hemorrhagic manifestations in both groups. The resulting corrected figures are portrayed graphically and referred to in the text without reference to the corrections or to the exceptions in treatment. *The corrections for exceptions proved to be small and sometimes were completely without effect on the rates. They do not alter at any point the basic differences between the groups from which conclusions are drawn.*

†The term statistically significant is used throughout the text to mean that the chances that two random samples from the same population would yield, on the basis of chance alone, differences as great as those observed and in the same direction are less than one in one hundred. In most instances the chances of obtaining these differences in two samples from the same universe are, in fact, very much less than one in one hundred: in the case of thromboembolic complications, they are less than one in one thousand.

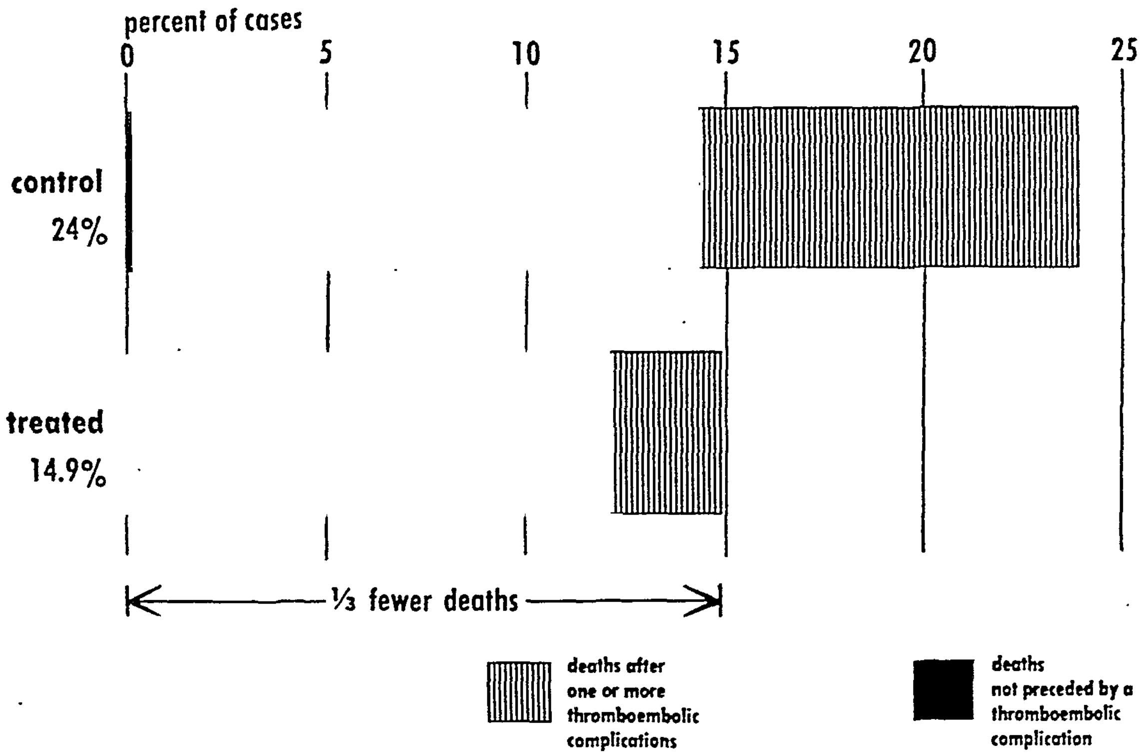

Fig. 1.—Patients dying in the control and treated groups under study.

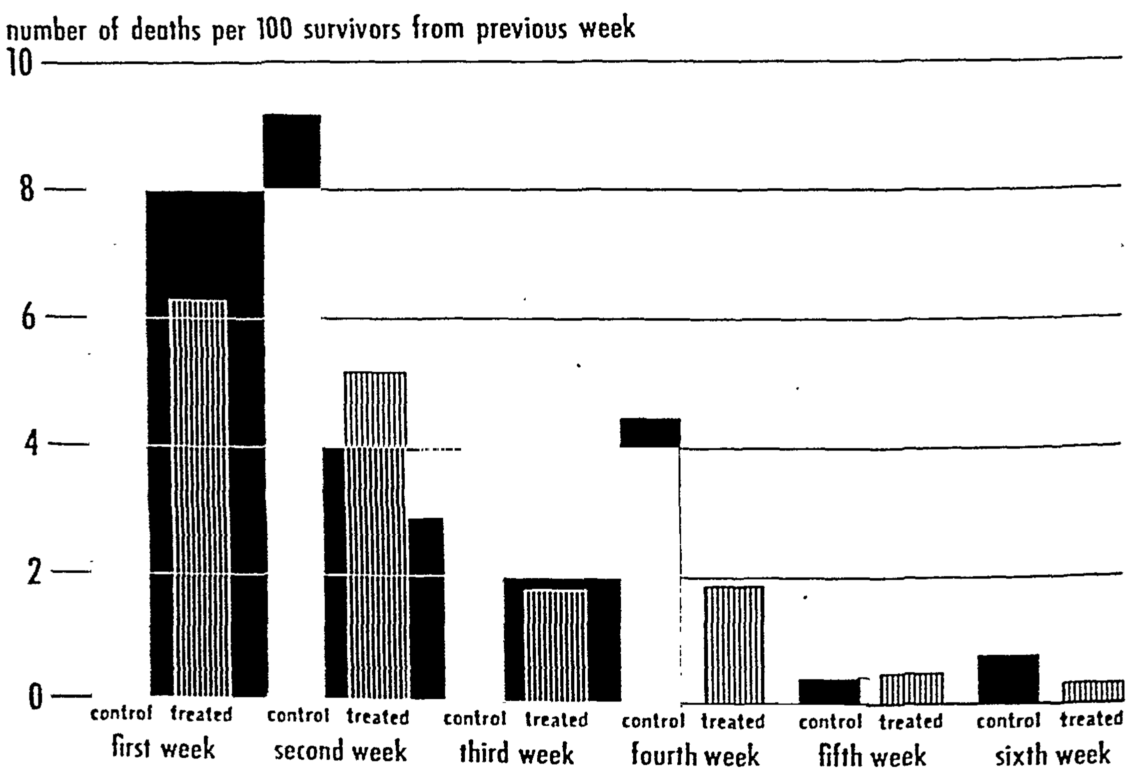

Fig. 2.—Comparison of death rates by week of illness in the control and treated groups.

The death rates by week of illness, as shown in Fig. 2, were highest during the first two weeks, but were still considerable during the third and fourth weeks. For each period the death rate for the control patients was found to be significantly greater than that for the treated group. These figures indicate, first, that anticoagulant therapy, if not used before, should be begun as late as the second or third week after a myocardial infarction has occurred, or later if complications have developed, and, second, that to give maximal protection, anticoagulant treatment should be continued for at least four weeks after the last thromboembolic episode.

Fig. 3 presents the death rates by major age groups. The greatest benefits in the reduction of mortality are in patients 60 years of age or older. These statistics show that the therapeutic effect of anticoagulants is sufficiently important to justify their use in the older age groups. Hemorrhagic complications have been so few and so mild throughout the entire study and the benefits of treatment of the older age groups are so pronounced that we do not hestitate to prescribe anticoagulants to older patients. It should be recognized, however, that older patients have a higher incidence of unrelated complications and that careful consideration of such factors is mandatory. While the crude death rates for patients under the age of 59 years in both the treated and the control groups did not show a significant difference, it will be seen in Fig. 6 that the incidence of thromboembolic complications is high in these age groups, and that the treated patients show a much lower incidence of thromboembolic complications. Such thromboembolic complications may not only be serious incidents in themselves, but they may result in such serious permanent disabilities as hemiplegia (following cerebral emboli), chronic venous insufficiency (following thrombophlebitis), or residual myocardial damage (following repeated myocardial infarction).

Fig. 4 shows the percentage of patients developing one or more thromboembolic complications. Twenty-five per cent of the control patients, in contrast to only 11 per cent of the treated patients, developed at least one such complication. This difference is statistically significant. However, of these treated patients, 3.5 per cent developed their first complication before they had received an anticoagulant* and 1.5 per cent developed their first thromboembolic complication during the first three days of anticoagulant therapy, a stage of treatment in which Dicumarol is ordinarily not fully effective. Thus, 5 per cent developed thromboembolic complications when anticoagulant therapy *could not* have been significantly effective and only 6 per cent developed thromboembolic complications while they were actually under the therapeutic effect of anticoagulant therapy.

The number of thromboembolic complications per one hundred cases is presented in Fig. 5. Among each 100 cases in the control group, thirty-six thromboembolic complications were diagnosed clinically, whereas among each 100 cases in the treated group, only fourteen thromboembolic complications were so diagnosed. In other words, patients in the "treated group" experienced slightly more than one-third as many thromboembolic complications as did patients in the control group, a contrast that is again highly significant statistically. This

*Included in this group are those who never received anticoagulants because of contraindications.

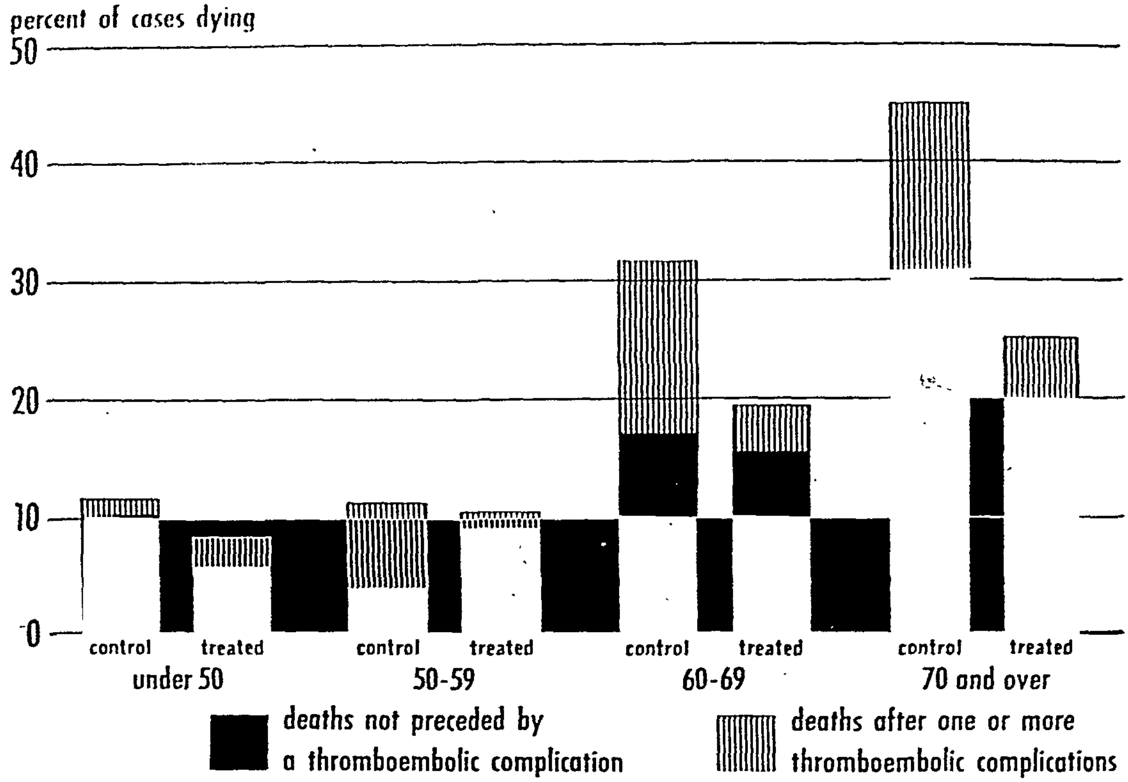

Fig. 3.—Death rates by age groups in the control and treated groups.

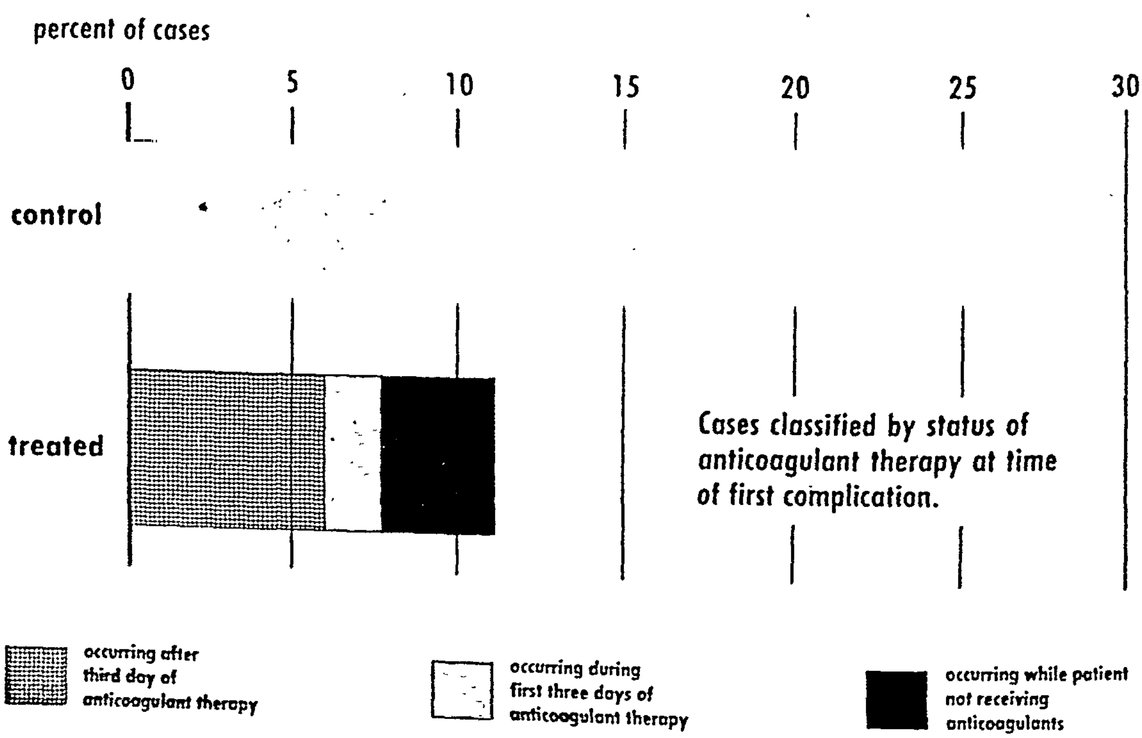

Fig. 4.—Patients developing one or more thromboembolic complications.

contrast is further emphasized by the following facts: It is noted that five thromboembolic complications per 100 cases developed while the patients were not receiving anticoagulant therapy and 2.5 thromboembolic complications per 100 cases developed during the first three days of anticoagulant therapy, when Dicumarol is not considered efficacious. Actually, then, only 6.5 thromboembolic complications per 100 treated cases occurred in patients who were under the full therapeutic effect of anticoagulant therapy. This figure includes complications in some patients whom we would not now consider to have been under adequate therapy at the time the complication occurred. Autopsies were conducted on 48 per cent of the patients dying among the 800. The autopsy records for these cases are being studied intensively and will yield further light on the effects of anticoagulant therapy on thromboembolic complications.

The highest incidence of thromboembolic complications among the control cases occurred in the age group between 50 and 59 years (Fig. 6); this is in distinct contrast to the death rate by age groups (Fig. 3). The explanation for this contrast may be that while the younger patients suffer numerous thromboembolic complications and while some of these complications result in serious damage, the younger patients are able to survive them. Thus, an individual under the age of 60 years may have three or four thromboembolic complications without a fatal episode, whereas an older patient may succumb to the initial attack and hence not have the opportunity of developing repeated thromboembolic attacks. This chart clearly indicates the value of anticoagulant therapy in preventing thromboembolic complications in all age groups. Within the treated group, a distinction is made between those actually receiving anticoagulants and those who were not receiving anticoagulants at the time of their thromboembolic complications. This further emphasizes the effects of anticoagulant therapy.

In Fig. 7 the rate of thromboembolic complications by week of illness is considered. The advantage in using anticoagulants is clearly demonstrated for each of the first four weeks of the illness. As is the case with deaths, the incidence of thromboembolic complications is highest in the second week, but is marked throughout the first four weeks. This again clearly indicates the importance of beginning anticoagulant therapy even as late as the second or third week following a myocardial infarction. Since it is impossible to predict from the condition of the patient during the first week whether he will develop thromboembolic complications during subsequent weeks or whether he will die from them, it is important to give anticoagulant therapy to all patients with coronary occlusion and myocardial infarction unless specific contraindications exist.

Fig. 8 indicates the types and locations of thromboembolic complications as they were encountered, and the effects of anticoagulant therapy in each group. Under the classification of secondary myocardial infarctions, there was evidence of extension of the original thrombosis in nine cases per 100 in the control series as against two cases per 100 in treated patients. There was infarction of new areas in the myocardium in 6.5 cases per 100 in the control series as against 2.5 among treated patients. Pulmonary emboli occurred in 9.4 cases per 100 among the control group as against 5.2 cases among the treated patients. More-

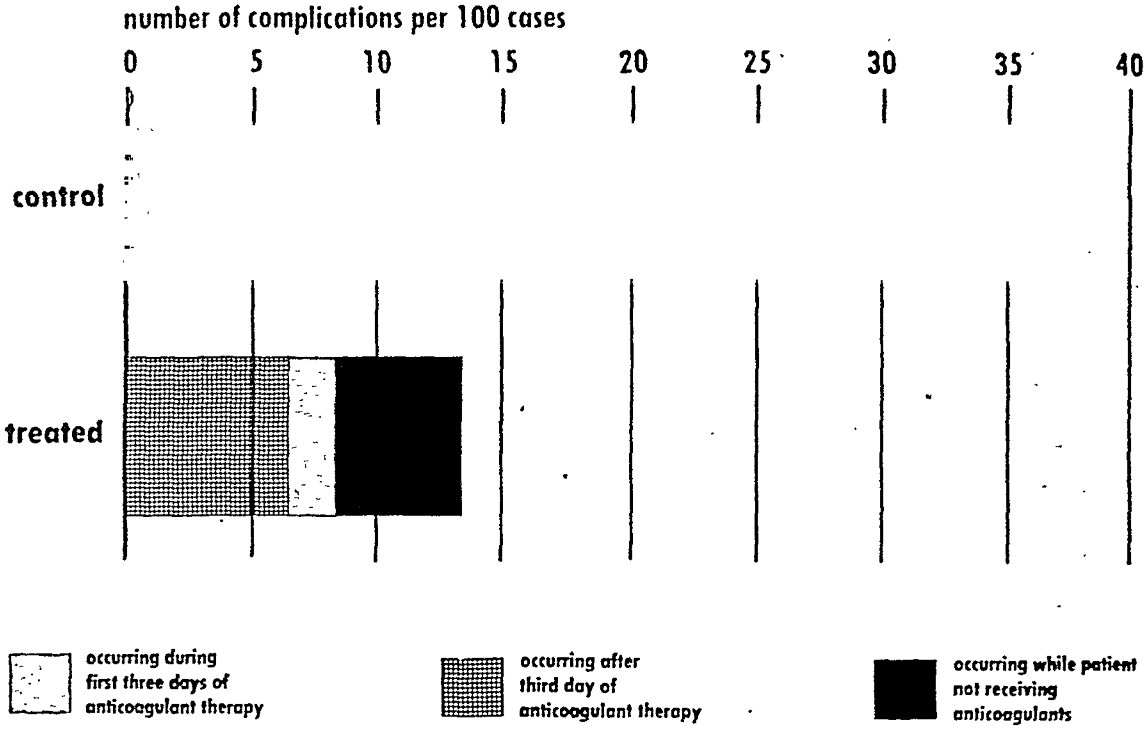

Fig. 5.—Number of thromboembolic complications in the control and treated groups.

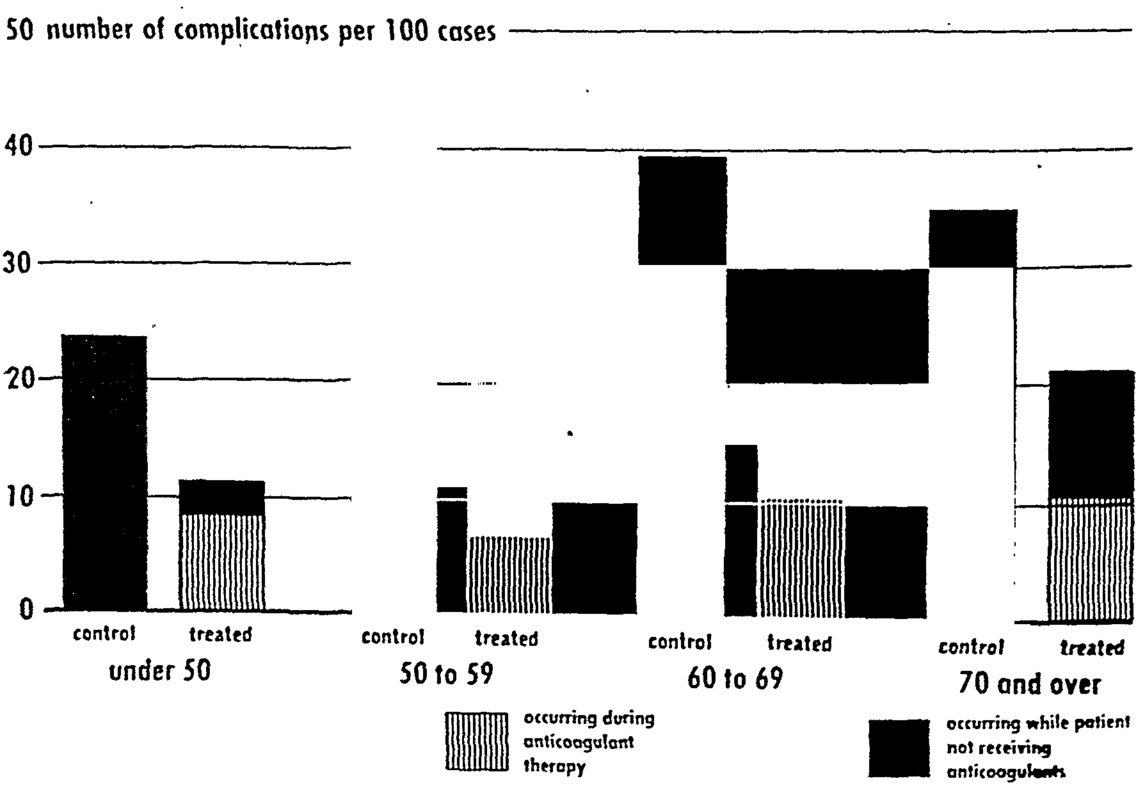

Fig. 6.—Rates of thromboembolic complications by age groups.

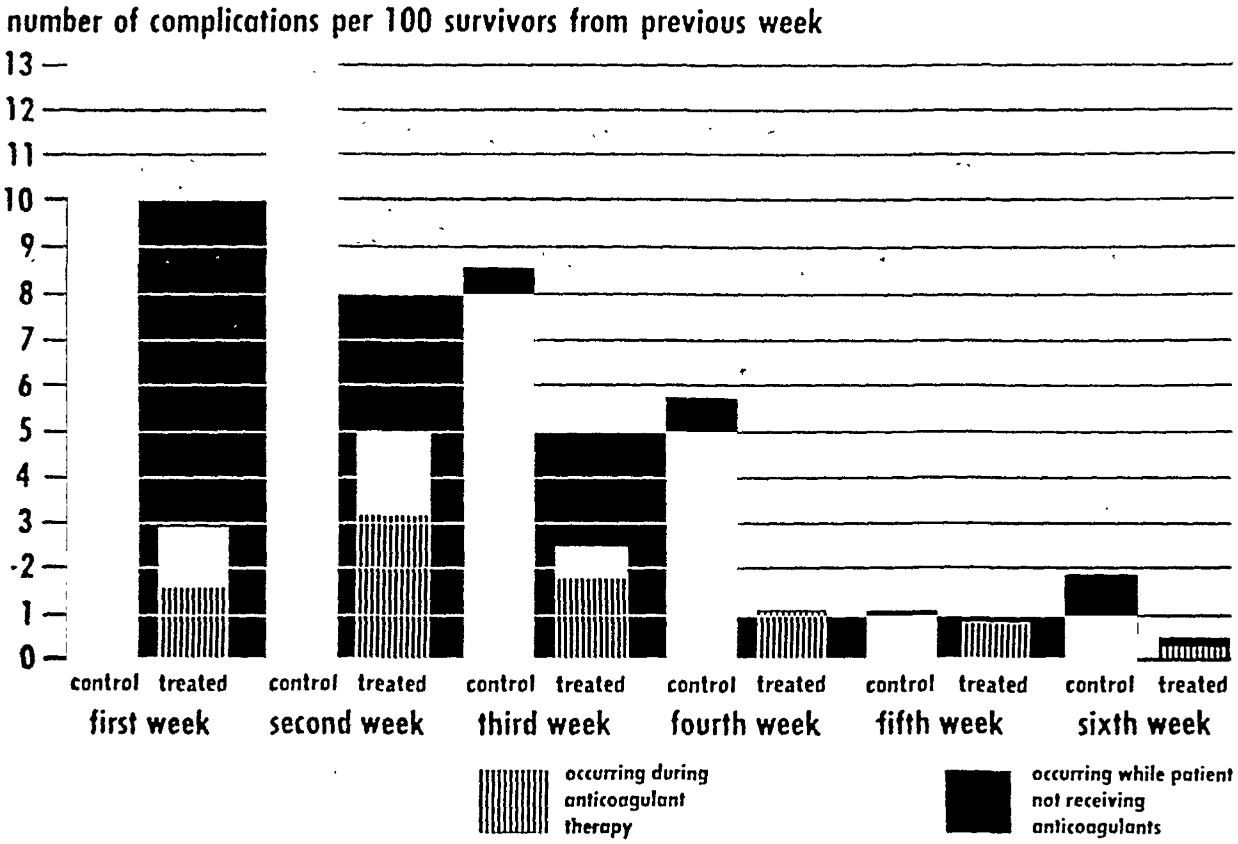

Fig. 7.—Rates of thromboembolic complications by week of illness.

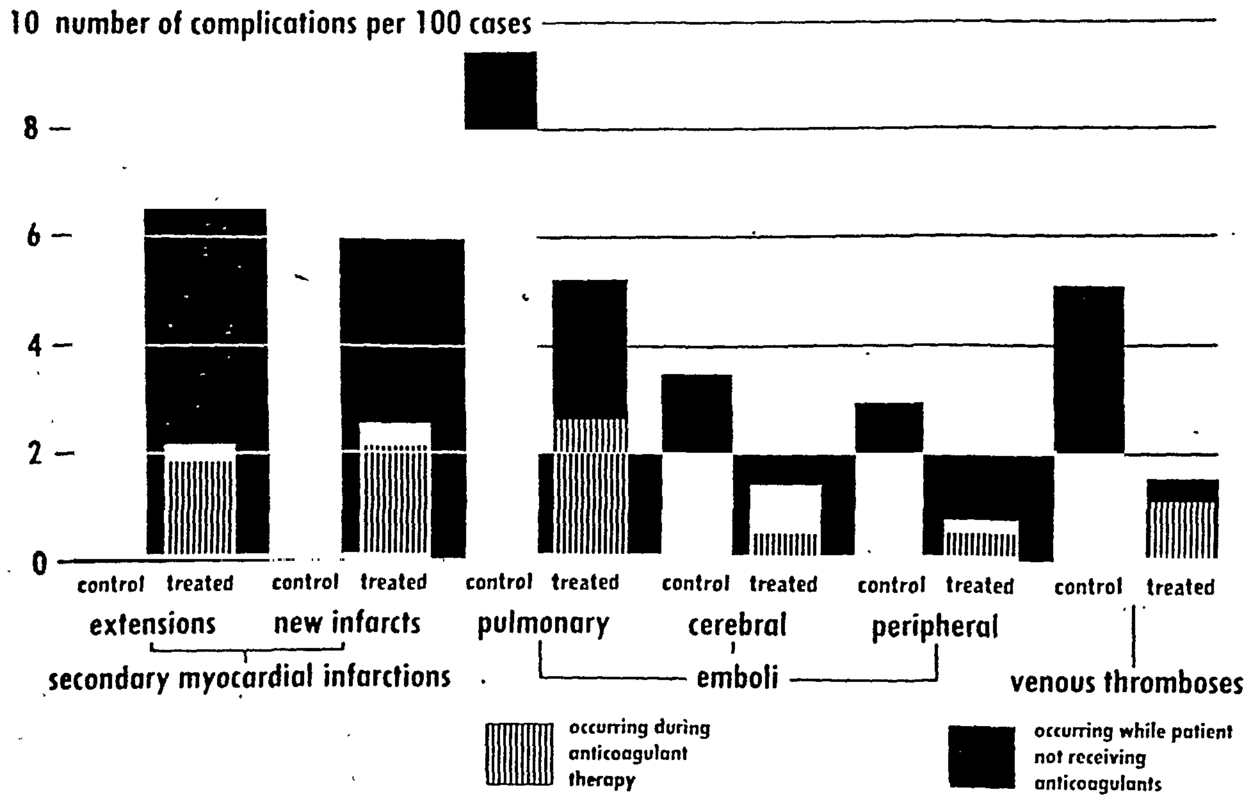

Fig. 8.—Types and locations of thromboembolic complications.

over, one-half of the so-called treated patients were not actually receiving anticoagulant therapy at the time they suffered their pulmonary embolism. Cerebral emboli occurred in 3.4 cases per 100 of the control patients as against 1.4 cases per 100 among the treated patients. Peripheral emboli developed in 3 cases per 100 of the control group as against 1 per 100 of the treated patients, and venous thromboses occurred in 5 cases per 100 of the control group as against less than 2 per 100 of the treated patients. Hence, it will be seen that at every site and with every type of complication, those receiving anticoagulant treatment in addition to conventional therapy had a distinctly better chance of escaping thromboembolic complications than those who received the conventional forms of therapy only.

The hazard of hemorrhagic manifestations resulting from anticoagulant therapy has been carefully reviewed (Fig. 9). It should be noted that hemorrhagic manifestations unrelated to anticoagulants numbered 6 per 100 cases in the control group. This is in comparison to a rate of slightly more than 12 per 100 cases among those patients who were classified as "odd day" or "treated" patients. It should be noted, however, that of these complications in the latter group, two in twelve developed in patients who were not under anticoagulant therapy when their hemorrhages occurred. In an additional three, the hemorrhages were known to have been the result of causes other than anticoagulants and not to have been aggravated by that therapy. The total hemorrhagic manifestations in the treated group which are known to have been the result of causes other than anticoagulants approached that found in the control group. An additional 7 per 100 cases, however, were believed to have been due to, or aggravated by anticoagulants. The incidence of severe hemorrhages resulting from anticoagulant therapy was extremely low. Of the thirty such hemorrhages clinically observed, fifteen (50 per cent) were mild in severity, fourteen (47 per cent) were moderately severe, and only one (3 per cent) was severe. The autopsy findings bearing on hemorrhagic phenomena are not yet ready for presentation, but those examined to date present no alarming picture of the hemorrhagic risks in anticoagulant therapy under proper controls. Blumgart and his co-workers,[6] working with dogs whose coronary arteries had been ligated, found that dicumarolized animals (in some instances with prothrombin times of 132 seconds) showed no increase of hemorrhages in the myocardium, endocardium, or pericardium when compared with nondicumarolized animals.

The sources of bleeding in relation to anticoagulants is demonstrated in Fig. 10. There is a definite incidence of hemorrhage among the control group in each of the categories except that for epistaxis. Hemorrhages due to causes other than anticoagulants also occur in three of the categories in the treated group. It will be noted that hemorrhages occurred more frequently in the treated group in all categories except that of hemoptysis. The explanation for the greater incidence of hemoptysis in control patients is that pulmonary infarction is much more common among these patients than among the treated patients.

The records of patients who received anticoagulant therapy and yet developed thromboembolic complications or died are being subjected to analysis in the Central Laboratory. It appears, on the basis of present experience, that

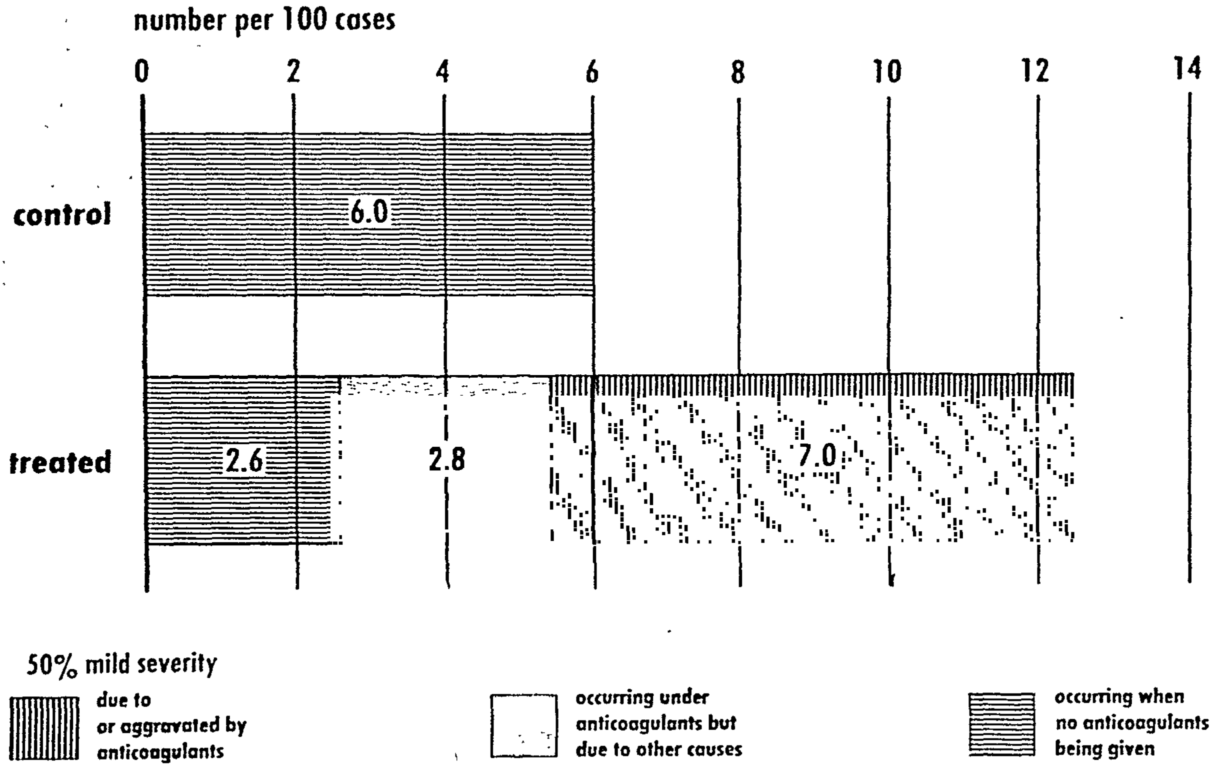

Fig. 9.—Relations of hemorrhagic manifestations to anticoagulants.

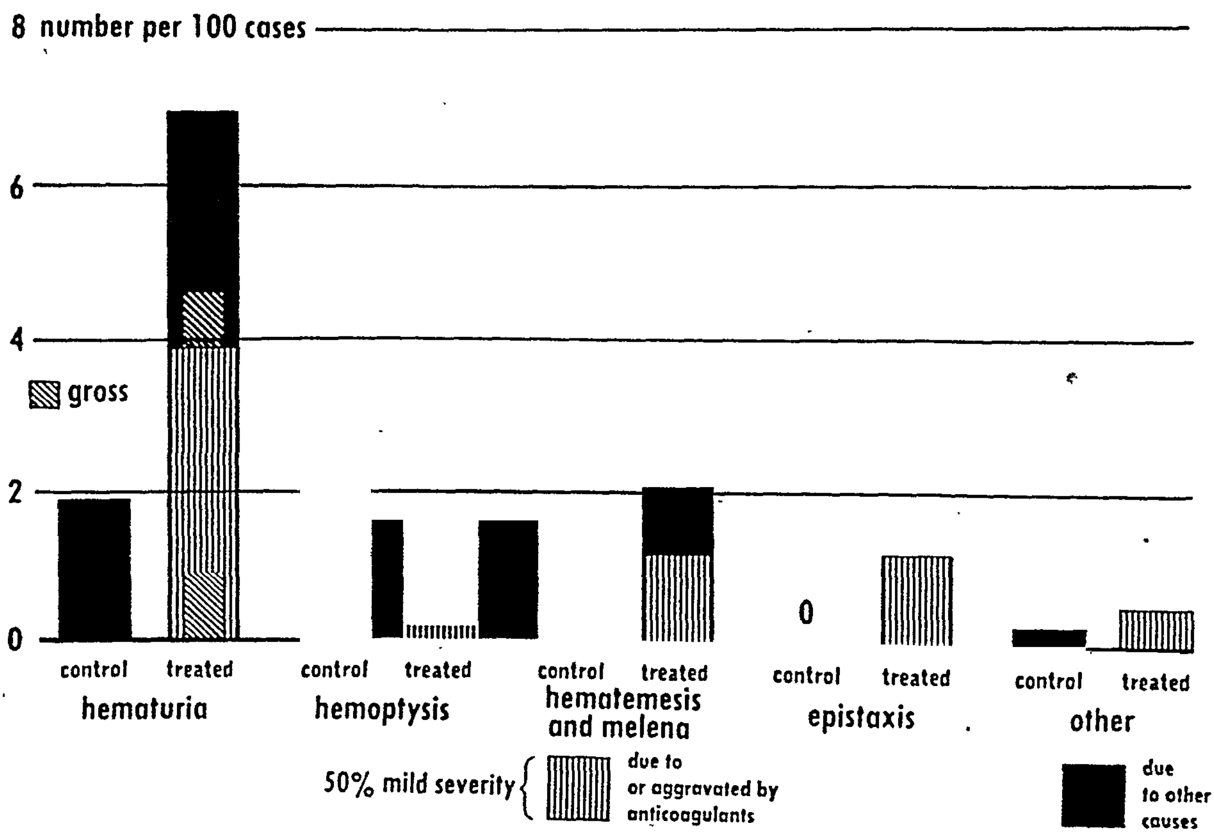

Fig. 10.—Sources of bleeding in hemorrhagic manifestations.

a considerable proportion of the failures occurred because the prothrombin time was not adequately prolonged. While there is at present a question as to what constitutes the minimal effective prothrombin time, it is our experience that a safe and effective therapeutic range is between 30 and 50 seconds by the Link-Shapiro modification of Quick's one-stage method. This range, as interpreted in our laboratory, would approximate a prothrombin activity of between 20 and 10 per cent. For heparin, the clotting time should be approximately three times normal. Although statistical evidence as to the relative incidence of thromboembolic complications at various prothrombin times (that is, at various levels of reduced prothrombin activity) is not yet available, a review of those cases in which thromboembolic complications occurred during the administration of Dicumarol reveals that of the thirty-eight complications* occurring under these conditions, only four occurred in patients whose prothrombin time is known to have been maintained at levels of 30 seconds or more for at least the three days preceding the appearance of the complication. Further analyses regarding this factor will be recorded in forthcoming publications. It is not sufficient to state that a patient has received anticoagulant therapy. Key questions which must be answered are: how much Dicumarol has been administered, and for how long; what levels of prothrombin time were obtained, and how consistently were these maintained? With this information it should usually be possible in the future to determine whether a failure was the responsibility of the drug or of those administering it.

SUMMARY

This report summarizes the results obtained by a preliminary statistical analysis of the first 800 cases studied by the Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis With Myocardial Infarction. In the analysis the incidence of deaths and of both thromboembolic and hemorrhagic complications has been compared in a "control" series of patients treated by conventional methods alone and in a series of "treated" patients who received anticoagulants (Dicumarol, heparin, or both) in addition to conventional therapy. The composition of the two groups was found to be essentially the same.

The rates of deaths and the number of thromboembolic complications per 100 cases have been calculated for the control and treated groups as a whole, by week of illness, by age of patient, and by type and location of the specific thromboembolic complication. The percentage of patients developing one or more complications has also been analyzed. The results in every category studied indicate that the use of anticoagulants improves strikingly the outlook of the patient suffering a coronary occlusion with myocardial infarction.

The incidence of hemorrhagic manifestations was also analyzed. It was found that about six minor or moderate hemorrhagic manifestations per 100 cases occur in patients not receiving anticoagulants. This incidence is about six per 100 higher in patients receiving anticoagulants.

*Complications for which the date is not accurately known and those occurring on days for which no prothrombin time is available are excluded from this total, but complications occurring in control cases when under anticoagulant therapy are included.

Although the minimum prolongation of the prothrombin time necessary to obtain a therapeutic effect from Dicumarol in each patient has not been established, it is our experience that a range of from 30 to 50 seconds, as measured by the Link-Shapiro modification of the Quick one-stage technique, produces a safe and an effective therapeutic level. This range of prothrombin times approximates a decrease in prothrombin activity to between 20 and 10 per cent as determined in our laboratory. In using heparin we attempt to prolong the clotting time of whole blood to approximately three times the normal value by the Lee-White technique. In only four cases of the entire series did thromboembolic complications occur when the prothrombin time had been maintained at a level of 30 seconds or above for at least three days prior to the occurrence of the complication.

CONCLUSIONS

On the basis of data compiled from 800 cases of coronary occlusion with myocardial infarction, it is concluded that:

1. Patients treated with anticoagulant therapy in addition to the conventional forms of therapy experience a death rate and incidence of thromboembolic complications during the first six-week period following an attack which are markedly lower than those experienced by patients treated solely by conventional methods.

2. Anticoagulant therapy should be used in all cases of coronary thrombosis with myocardial infarction unless a definite contraindication exists.

3. In the absence of other hemorrhagic states, the hazards from hemorrhage due to anticoagulants are not sufficient to contraindicate their use in the treatment of coronary occlusion providing there are facilities for adequate laboratory and clinical control.

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SOME EFFECTS OF QUINIDINE SULFATE ON THE HEART AND CIRCULATION IN MAN

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WITH the development of the technique of right heart catheterization for the determination of cardiac output[1,2,3] and for the recording of right heart pressures,[4] it is possible to study the action of certain drugs on the dynamics of the circulation in man. Drugs best suited to this type of investigation are those which can be administered in a single dose and which manifest their maximum effect in one to three hours. Quinidine fulfils these criteria. Moreover, the effects of this drug on the circulation in man, aside from its action on arrhythmias, have been incompletely studied.

The pharmacology of quinidine was first described in 1893, and the drug was introduced into clinical use in 1918.[5] During the next ten years clinical and experimental investigations were primarily concerned with the effect of quinidine on auricular fibrillation and other arrhythmias and the mechanisms by which normal rhythm was restored. Some observations have been made on heart rate, blood pressure, peripheral circulation, stroke volume, cardiac output, and contractility of heart muscle. Most of these studies have been made on isolated heart preparations or on animals, but a few have been made on man. Extensive studies have been made in man on the electrocardiographic changes produced by the drug.

In human and animal experiments, Lewis and associates[6,7,8] noted that in auricular fibrillation quinidine slowed the auricular but increased the ventricular rate. In dogs with normal sinus rhythm, some observers have found an increase[9,10,11] and some, a slowing,[12] while others noted no change in heart rate.[13] Starr and co-workers[14] reported an increase in heart rate in human subjects with normal sinus rhythm.

Most investigators, using intravenous quinidine in animals, found a fall in blood pressure,[13,15-18] but one group noted a rise.[9] Levy[19] has stated that there is no significant effect on the blood pressure in man. The effect of quinidine on the peripheral circulation has been reported by two groups of investigators.[15,16] In evaluating the fall in blood pressure produced by quinidine in animals, both

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groups suggest an action of the drug on the peripheral vessels. In addition, Jackson and associates[15] were able to demonstrate an increase in leg volume and a fall in pulmonary artery pressure coincident with the fall in systemic blood pressure. They state, ". . . it is to be noted that the dilatation of the vessels of the hind limb with the consequent increase in volume and the dilatation of the pulmonary arterioles and capillaries both indicate that the drug possesses a distinct peripheral action on the circulation. . . ."

A diminution in stroke volume and work per beat has been reported by Starr and his co-workers.[14] They also found no significant change in cardiac output in man, using the ethyl iodide method of cardiac output determination. However, another group,[9,10] working with dogs, found an increase in cardiac output.

Most investigators have reported a weakening of the contraction of the animal heart following quinidine.[12] Cohn and Levy[13] demonstrated, by means of the myocardiograph, an increase in the amplitude of the recorded cardiac contraction.

Quinidine produces certain well-known changes in the electrocardiogram.[6,7,13,16,17,20-22] The majority of investigators describe prolongation of the Q-T interval and T-wave changes. In addition, widening of the QRS complex sometimes occurs.[17] Reports are contradictory as to the effects of the drug on the P-R interval. Prolongation of this interval was noted by Lewis and associates,[6,7] but Gold and co-workers[11,17] found that it remained the same or became shorter.

METHOD OF STUDY

The present study is concerned with the effect of quinidine sulfate on the circulation in subjects with an essentially normal cardiovascular status and in patients with heart disease. Quinidine sulfate, 0.8 Gm. by mouth, was given in a single dose on the basis that this amount represents the maximum effective single oral dose of this drug, as originally suggested by Lewis[7] and recently re-emphasized by Gold.[23] In the treatment of arrhythmias the maximum therapeutic effect following the administration of the dose indicated was noted one and one-half to two and one-half hours after ingestion[17,23] and the plasma concentration was found to reach its height in two to four hours.[24,25] The electrocardiographic changes have been described as early as fifteen minutes after oral administration of quinidine.[22] Any circulatory effects can, therefore, be expected during the first three hours after ingestion of the drug.

Changes in the circulation were measured by the technique of right heart catheterization. The measurements obtained include right heart pressures and cardiac output, as well as peripheral artery pressures, blood volume, and electrocardiograms.

Pressure changes in the right auricle, right ventricle, and pulmonary artery were recorded by means of an intracardiac catheter attached to a Hamilton manometer.[4] Femoral or brachial artery pressures were recorded by direct intra-arterial needle and a Hamilton manometer. The systolic, diastolic, and mean pressure values represent the average figures obtained by analyzing each heart

beat during two complete respiratory cycles, as described by Bloomfield and associates[4] and more recently by Werkö.[26] Heart rate was computed from the electrocardiogram. Cardiac output and cardiac index were determined by the direct Fick principle.[2,27] Total peripheral resistance was calculated according to the formula:

$$R = \frac{(\textit{Arterial Mean Pressure Minus Right Auricular Mean Pressure}) \times 1{,}332}{\textit{Cardiac Output Per Second}}$$

and expressed as dynes, seconds, cm.$^{-5}$. Pulmonary resistance was computed using pulmonary artery mean pressure. Blood volume determinations were made by the dye method as modified by Noble and Gregersen.[28] Standard Leads I, II, and III were recorded by means of the Cambridge electrocardiograph.

PROCEDURE

All patients studied were in the resting state. The majority were fasting, but a few took liquids two hours before the study was begun. Most of the patients received 0.1 Gm. of phenobarbital the evening before the procedure, and 0.1 to 0.2 Gm. of pentobarbital and 0.03 Gm. codeine sulfate, orally, one to two hours before any determinations were made. A test dose of 0.2 Gm. of quinidine sulfate was given the day preceding the study.

Before the introduction of the catheter or the intra-arterial needle, a control electrocardiogram (standard Leads I, II, and III) was taken. The catheter was placed with the tip in the right auricle and the brachial or femoral artery needle was inserted. At least thirty minutes elapsed with the patient at rest before control pressures were recorded. Pressure tracings were made from the right auricle, then (after the catheter tip was advanced) from the right ventricle, and in some instances, from the pulmonary artery, simultaneously with peripheral artery tracings and standard Lead II of the electrocardiogram. The control cardiac output was then determined with the catheter in the right ventricle. In the majority of cases the catheter tip was left in the right ventricular cavity for the rest of the study in order to avoid excessive manipulation. A control blood volume, by means of the ten-minute sample technique,[28] was measured.

The patient then received 0.8 Gm. of commercial quinidine sulfate by mouth. Every half hour for the next two to three hours, right ventricle and peripheral artery pressure tracings and the three standard leads of the electrocardiogram were recorded. Cardiac output determinations were done one hour and two hours after quinidine sulfate unless the tracings showed a marked fall in systemic blood pressure. In this event, cardiac output was determined immediately. The study was concluded two and one-half to three hours after the administration of the drug, with a second measurement of blood volume.

Types of Patients Studied.—The patients studied were of two types: (1) those with essentially normal circulation, and (2) those with cardiovascular disease. Eight normal subjects and twelve patients with heart disease were stud-

ied by the catheterization technique. Their control and postquinidine values are given in Tables II, III, IV, and V, respectively.

The criteria used for diagnosis of the cardiac patients were those adopted by the American Heart Association.[29] The functional and therapeutic evaluation represents the status of the patient at the time of the study. It became obvious, however, on examination of the control physiologic data (Tables IV and V) that, in addition, a tentative physiologic classification could be set up. This was done in an effort to place these patients in the proper perspective as far as the natural history of their disease is concerned. Variations in systemic flow (cardiac output) and right heart pressures comprise the basic criteria for the physiologic classification offered. Admittedly,[29, p. 71] the standard functional classification, based on clinical tests, is of limited accuracy in determining early abnormalities of cardiac function. This is not unexpected, as it seems logical to assume that abnormal variations in function appear at a much earlier stage in cardiac disease than do the symptoms indicative of a breakdown in functional capacity. This physiologic classification is somewhat arbitrary, but actual measurement of pressures and blood flow should provide a more accurate index of circulatory function than the clinical criteria of the standard classification.

Group A is composed of two patients with normal cardiac output (3.12 ± 0.4 liters per minute per square meter of body surface)[2] but elevation of either systolic or diastolic right ventricular pressures (upper limit of normal values 30/5).[4]

Group B is represented by one patient with a high cardiac output and elevation of right ventricular systolic pressure. All of the patients in Groups A and B are those with the American Heart Association classification of I,A.

Group C. A patient (S. H.) with a low cardiac output and elevated right ventricular pressures, who had never received digitalis, and was classified III,C, represents Group C.

Group D. These four patients had been maintained on digitalis for a considerable period of time and in spite of this were still in Class III,C. All except one had low cardiac outputs and all had elevated right ventricular pressures. Although the cardiac output value of 3.18 liters per minute per square meter of body surface of Patient T. C. is within the normal range, the patient had cor pulmonale which, in its early stages, is often characterized by a high cardiac output.[3,31] Hence, this figure of 3.18 liters per minute per square meter might be construed as a low cardiac output for this cardiac condition.

Group E. These four patients, classed as II,B, and all well digitalized, had low or low-normal cardiac outputs and normal right ventricular pressures. In addition, two of the four showed markedly increased blood volumes. It should be stated that clinically this group of patients had had severe cardiac decompensation from which they had recovered. Apparently, therefore, the only residual dynamic defect consistently present was that of systemic flow, as the right heart pressures were normal.

As will be described, there were no changes in cardiac rhythm following quinidine administration. This study, therefore, is concerned with those effects of quinidine on the heart and circulation other than those associated with alterations in cardiac rhythm.

The Influence of Cardiac Catheterization on Hemodynamics.—An indwelling catheter in the right heart causes a negligible effect on the circulation.[1] For the interpretation of the results of the present study, however, it was important to have a control series of observations on subjects who went through the same procedure except for the administration of quinidine; specifically, the catheterization, the intra-arterial indwelling needle, and the period of prolonged recumbency.

Such a series was that in which a study was made of positive pressure breathing.[26,30] The procedure followed during that investigation was sufficiently similar to the one used in the present quinidine study to warrant comparison. The patients were kept three to four hours on a fluoroscopic table which was covered with a sponge rubber mattress. They received the same premedication and were also in the fasting state. Control observations on blood pressures and cardiac outputs were made at the beginning and at the end of each case study. The second determination, some two to two and one-half hours later, was always preceded by a period of absolute rest, usually twenty to thirty minutes, during which the patient was undisturbed by any manipulations. Comparison of these two sets of observations gives an indication of the variations produced by the experimental method. Results are shown in Table I. It is obvious that in the normal subjects the variation in both arterial and right ventricular pressures was small. In the majority of normal subjects there was a small rise in systolic and diastolic arterial pressures and a slight tendency toward a fall in right ventricular

TABLE I. HEMODYNAMIC CHANGES OBSERVED OVER A PERIOD OF TWO AND ONE-HALF HOURS IN A GROUP OF SUBJECTS NOT RECEIVING MEDICATION

	RANGE OF VARIATION* DURING OBSERVATION PERIOD IN:	
	GROUP OF ELEVEN SUBJECTS WITH NORMAL CIRCULATION	GROUP OF EIGHT CARDIAC PATIENTS
Arterial blood pressures (mm. Hg)		
Systolic	−9 to +13	−3 to +38
Diastolic	−4 to +11	−1 to +15
Mean	−4 to +12	−4 to +27
Right ventricular pressures (mm. Hg)		
Systolic	−2 to +3	−1 to +16
Diastolic	−2 to +4	−4 to +9
Mean	−3 to +2	−6 to +13
Heart rate (beats/min.)	−15 to +10	−3 to +15
Cardiac output (per cent)	−15 to +14	−15 to +11

*With respect to first control determination.

systolic and diastolic pressures. In the cardiac group the tendencies were the same, but the magnitude of the changes was greater when they occurred. Variations in heart rate were not greatly different in the two groups. The changes in cardiac output were grouped evenly around the zero point. The range of variation in both groups fell between −15 per cent and +14 per cent, which is the range of variation expected by this method.

RESULTS

A. *Subjects With Essentially Normal Circulation.*—

1. *The Effect of Quinidine on Arterial and Right Ventricular Blood Pressures (Table II)*: Of the eight subjects studied, four (R. K., F. N., H. W., and J. S.) showed a significant fall in systolic, diastolic, and mean arterial pressures. The smallest falls were, in millimeters of mercury, −18 systolic and −12 diastolic, and the greatest falls were −64 systolic and −33 diastolic. The right ventricular pressures were recorded in only two of these four patients and showed no change. In addition, one subject (M. R., Table II) demonstrated a significant rise (systolic +37, diastolic +16 mm. Hg) in arterial blood pressures followed by an equally large fall (systolic −28, diastolic −9 mm. Hg). There was no change in the right ventricular pressures. Three subjects showed no change in arterial pressures. Of these, two had right ventricular pressures recorded and neither showed any change. The fall in arterial blood pressure was first noted at one to one and one-half hours and reached its maximum two hours after the drug was administered. In this acute experiment the duration of the fall in blood pressure could not be determined as the majority of the patients were only studied from two to two and one-half hours after the administration of the drug.

Comparison with the control data in Table I shows that the arterial pressure fall in these four of eight subjects was much beyond the normal range of variation and was presumably a quinidine effect.

2. *The Effect of Quinidine on Heart Rate (Table II)*: Seven subjects were followed for changes in heart rates. Five showed no change, and two (O. S. and J. S.) showed an increase in rate. One (O. S.) of these two had no change in blood pressure; the increase in rate of the other (J. S.), however, occurred at the time of the fall in arterial blood pressure.

3. *The Effect of Quinidine on Cardiac Output (Table III)*: Cardiac output was determined in five of the eight normal subjects and no change was noted. Three of these five subjects had significant falls in arterial blood pressure and two had no change.

4. *The Effect of Quinidine on Peripheral Resistance (Table III)*: Since one of the two variables used for the calculation of peripheral vascular resistance, namely, the cardiac output, was found not to change significantly in the normal subjects, it is only in the cases where the mean arterial pressure decreased that the vascular resistance was reduced. There were three such subjects (F. N., M. R., and H. W.) out of the five where the computation could be made. The peripheral resistance in these subjects was reduced, respectively, by 33 per cent,

TABLE II. THE EFFECT OF QUINIDINE ON HEART RATE AND BLOOD PRESSURES IN EIGHT SUBJECTS WITH ESSENTIALLY NORMAL CIRCULATION

CASE	TIME (MIN.)	HEART RATE (PER MIN.)	BRACHIAL ARTERY (MM. HG)			RIGHT VENTRICLE (MM. HG)	
			SYSTOLIC	DIASTOLIC	MEAN	SYSTOLIC	DIASTOLIC
H. C., male, 39 years; B. S. A. 1.82; infectious hepatitis, subsiding	Control	80, 75, 75, 80	144	82	104	—	—
			150	85	110	—	—
	30*	90	161	93	123	—	—
	60	90	137	77	100	—	—
	90	90	138	79	102	—	—
	125	80	140	80	105	—	—
F. N., male, 46 years; B. S. A. 1.76; bronchiectasis	Control	68, 75	110	68	87	27	6
	29*	62	115	70	91	25	6
	44	71	102	63	80	—	—
	67	83	94	58	72	28	6
	87	78	88	55	69	—	—
	117	78	87	53	67	24	5
	127	71	85	52	66	—	—
M. R., male, 49 years; B. S. A. 1.70; postpneumonia	Control	62, 65, 65	104	60	80	23	5
			125	73	93		
	28*	68	136	78	102	20	3
	53	62	147	80	107	—	—
	63	65	152	82	108	23	6
	88	75	113	69	86	18	4
	133	68	87	57	70	16	2
	148	71	92	63	77	—	—
W. M.,† male, 46 years; B. S. A. 1.74; central nervous system syphilis and hemiparesis	Control	85, 83, 78	155	86	115	—	—
	12*	83	156	87	118	25	6
	30	75	150	86	114	28	5
	71	85	149	84	109	22	5
	97	85	153	88	114	—	—
	120	90	153	88	114	—	—
H. W., male, 44 years; B. S. A. 1.71; polyneuritic syndrome	Control	83, 88, 88	134	85	107	—	—
			145	90	113	—	—
	24*	88	139	86	109	—	—
	54	88	130	85	105	—	—
	89	88	76	55	59	—	—
	124	83	92	66	79	—	—
R. K., male, 49 years; B. S. A. 1.67; gonococcal arthritis, subsiding	Control	75, 75, 75	112	66	85	26	4
			118	68	89		
	30*	75	119	73	93	26	3
	73		90	50			
J. S., male, 53 years; B. S. A. 1.69; pulmonary fibrosis and emphysema, bronchiectasis	Control	83, 115, 115	93	66	79	30	1
			89	64	75		
	25*	107	104	71	86	—	—
	43	107	92	66	78	26	1
	55	115	96	69	80	27	2
	95	125	74	52	62	—	—
	123	125	73	53	63	—	—

TABLE II. THE EFFECT OF QUINIDINE ON HEART RATE AND BLOOD PRESSURES IN EIGHT SUBJECTS WITH ESSENTIALLY NORMAL CIRCULATION—(CONTINUED)

CASE	TIME (MIN.)	HEART RATE (PER MIN.)	BRACHIAL ARTERY (MM. HG)			RIGHT VENTRICLE (MM. HG)	
			SYSTOLIC	DIASTOLIC	MEAN	SYSTOLIC	DIASTOLIC
O. S., male,	Control	75, 78, 71	116	69	91	28	3
33 years;			117	65	89		
B. S. A. 1.77;	27*	83	114	65	88	23	5
chronic	45	71	119	70	90	23	5
alcoholism,	103	107	110	68	91	28	6
postpneu-	125	107	114	68	92	27	−1
monia	140	120	111	68	91	—	—

*Time after quinidine administration.
†Femoral artery pressures during entire study.
B.S.A. = body surface area in square meters.

TABLE III. THE EFFECT OF QUINIDINE ON CARDIAC OUTPUT, PERIPHERAL RESISTANCE, AND BLOOD VOLUME IN FIVE SUBJECTS WITH ESSENTIALLY NORMAL CIRCULATION

CASE	TIME (MIN.)	CARDIAC INDEX (1/MIN./SQ. M.)	OXYGEN COMSUMPTION (C.C./MIN.)	A-V O_2 DIFF. (VOL. %)	PERIPHERAL RESISTANCE (DYNES, SEC., CM^{-5})	BLOOD VOLUME	
						TOTAL (C.C.)	PLASMA (C.C.)
H. C., male, 39 years; B. S. A.	Control	5.13	281	3.0	894	6200	3710
1.82; infectious	60*	4.43	273	3.4	995		
hepatitis, sub-	125	4.76	277†	3.2	945		
siding	145	4.92	277†	3.1	—	5850	3510
F. N., male, 46 years; B. S. A.	Control	2.91	266	5.2	1355	—	—
1.76; bronchiectasis	117*	3.28	249	4.3	907	—	—
M. R., male, 49 years; B. S. A.	Control	2.71	244	5.3	1500	3640	1950
1.70; post-	88*	2.49	227	5.3	1630		
pneumonia	125	2.95	261	5.2	1100	4120	2190
W. M., male, 46 years; B. S. A.	Control	3.66	204	3.2	1393	—	—
1.74; central	71*	3.50	210	3.5	1440	—	—
nervous system syphilis and hemiparesis	120	3.11	195	3.6	1665	—	—
H. W., male, 44 years; B. S. A.	Control	3.19	262	4.8	1620	—	—
1.71; poly-	54*	3.42	275	4.7	1440	—	—
neuritic syndrome	124	2.83	242	5.0	1308	—	—

*Time after quinidine administration.
†Assumed oxygen consumption (average of values obtained in first and second cardiac outputs).
B. S. A. = body surface area in square meters.

27 per cent, and 19 per cent. In the two other subjects (H. C. and W. M.) with only small changes in cardiac output and mean blood pressure, the peripheral resistance increased by 11 per cent and 20 per cent, respectively. Since the accepted variation in cardiac output is plus or minus 15 per cent for this study, it is clear that in the expression of peripheral resistance, as here calculated, a fluctuation of the same magnitude can be expected if the mean arterial pressure does not change. Hence, in the two subjects with unchanged blood pressure, these variations in peripheral resistance probably represent fluctuations within the expected range. On the other hand, in the subject H. W. a fall in peripheral resistance of 19 per cent is probably a true expression of a change in the peripheral arteriolar bed, as it was associated with a fall in blood pressure.

5. *The Effect of Quinidine on Blood Volume* (*Table III*): In one (H. C.) of the two patients studied, total blood volume was reduced by 5 per cent after quinidine, and in the other subject (M. R.), it was increased by 13 per cent. These changes are probably not significant.

Discussion of Changes Produced by Quinidine in Normal Subjects (*Tables II and III*).—The only significant change in the hemodynamics of normal circulation was a fall in arterial blood pressure in one-half the cases studied. Subject M. R. had a rise in blood pressure during the early phase of the investigative period, and from this higher level of pressure there developed a marked fall which persisted for one hour. In three subjects a fall in peripheral resistance was associated with the fall in blood pressure, suggesting an action of quinidine on the peripheral vascular bed. Right ventricular pressures were not altered by quinidine.

There were no significant changes in heart rate, cardiac output, and blood volume.

B. *Patients With Cardiovascular Disease.*—

1. *The Effect of Quinidine on Arterial and Right Ventricular Blood Pressures* (*Table IV*): The data presented in Table I were also used as a guide for the interpretation of significant changes in blood pressures, heart rate, and cardiac output in these cases of cardiac disease.

Group A: One (R. C.) of the two patients showed a fall in arterial systolic, diastolic, and mean pressures, while the other (M. I.) showed no change. Right ventricular pressures were recorded in both instances and were not altered.

Group B: The one patient (P. B.) in this group showed a fall in arterial systolic, diastolic, and mean pressures. The right ventricular systolic pressure fell; the diastolic pressure did not vary.

Group C: This patient (S. H.) showed one of the most marked falls in arterial blood pressures, 65 mm. Hg systolic and 32 mm. Hg diastolic. Only one other patient (H. I.) had a larger fall in diastolic pressure, 46 mm. of mercury. A concomitant fall occurred in the right ventricular systolic pressure; the right ventricular diastolic pressure did not change.

TABLE IV. THE EFFECT OF QUINIDINE ON HEART RATE AND BLOOD PRESSURES IN TWELVE PATIENTS WITH CARDIOVASCULAR DISEASE

CASE	TIME (MIN.)	HEART RATE (PER MIN.)	BRACHIAL ARTERY (MM. HG)			RIGHT VENTRICLE (MM. HG)	
			SYSTOLIC	DIASTOLIC	MEAN	SYSTOLIC	DIASTOLIC
Group A. Normal Cardiac Output; Elevated Right Ventricular Pressures							
M. I., female, 23 years; B. S. A. 1.71; interventricular septal defect; NSR; IA	Control	60, 62, 71, 68	114	59	74	21	8
			103	62	72		
			103	63	70		
			(By sphygmomanometer)				
	30*	80	110	70	—	—	—
	65	65	112	70	—	18	8
	85	85	118	72	—	19	7
	112	70	118	70	—	20	8
R. C., male, 14 years; B. S. A. 1.66; RHD, EH, MS. MI, AI, SA; incomplete A-V block, IA	Control	70, 68	130	65	92	38	5
	26*	83	137	75	103	—	—
	60	70	144	69	100	40	10
	110	93	68	42	56	—	—
	125	100	82	45	60	41	3
Group B. High Cardiac Output; Elevated Right Ventricular Pressures							
P. B., male, 55 years; B. S. A. 1.72; Unk. HD, EH, NSR, IA; ? cor pulmonale	Control	115, 100, 100, 100	146	85	112	36	5
			142	82	108	—	—
	57*	100	106	66	85	25	3
	119	88	125	73	96	21	3
Group C. Low Cardiac Output; Elevated Right Ventricular Pressures; No Digitalis							
S. H.,† male, 57 years; B. S. A. 1.50; HCVD, ASHD, EH, CS, MF, NSR, CI, PND, LBBB, IIIC	Control	65, 75, 71	197	108	135	33	7
	30*	70, 80	139	76	100	25	3
	42	80	139	80	102	21	3
	82	83	132	76	98	19	4
	94	95	148	83	112	—	—
	107	100	157	86	111	—	—
Group D. Low or Normal Cardiac Output; Elevated Right Ventricular Pressures; Digitalized							
H. I., male, 51 years; B. S. A. 1.70; HCVD, EH, NSR, CI, IIIC; arteriolar nephrosclerosis	Control	93, 88, 88	218	125	158	60	9
			222	130	162		
	10*	88	218	122	156	56	5
	35	83	218	125	158	—	—
	40	83	217	125	154	51	6
	60	88	218	125	151	43	9
	95	86	219	117	156	56	8
	110	86	216	114	152	56	8
	127	86	230	117	154	41	11
	145	80	187	96	129	—	—
	155	78	176	90	118	39	7
	160	80	161	82	110	—	—

Continued on next page. All footnotes appear at end of table.

TABLE IV. THE EFFECT OF QUINIDINE ON HEART RATE AND BLOOD PRESSURES IN TWELVE PATIENTS WITH CARDIOVASCULAR DISEASE—(CONTINUED)

CASE	TIME (MIN.)	HEART RATE (PER MIN.)	BRACHIAL ARTERY (MM. HG)			RIGHT VENTRICLE (MM. HG)	
			SYSTOLIC	DIASTOLIC	MEAN	SYSTOLIC	DIASTOLIC
H. C., male, 45 years; B. S. A. 1.85; coarctation of the aorta; EH, NSR, PND, CI, IIIC	Control	75, 71, 71, 68	225	108	145	65	12
			118‡	90‡	103‡		
			224	120	151		
	35*	71	234	123	160	67	6
	58	68	234	122	157	65	—
	86	71	234	123	156	65	9
	115	75	226	115	149	41	3
	133	75	222	120	153	36	2
			110‡	81‡	95‡		
	138	71	215	107	138	—	—
			108‡	83‡	94‡		
	148	68	219	110	144	36	3
	156	68	216	106	138	—	—
J. L., male, 63 years; B. S. A. 1.43; RHD, EH, MS, MI, AI, NSR, CI, IIIC	Control	68, 68, 71, 71	150	79	109	38	2
			147	77	106		
	29*	78	134	70	97	—	—
	54	71	109	56	73	—	—
	62	75	101	55	74	—	—
	92	75	99	53	72	—	—
	97	75	102	56	75	26	−1
	132	75	109	59	82	25	2
T. C., male, 49 years; B. S. A. 1.62; cor pulmonale; EH, NSR, CI, IIIC; Pulm. F and E	Control	115, 107, 115	115	74	89	110	7
	55*	115	85	49	62	93	8
	73	115	—	—	—	100	5
	88	115	101	63	79	96	8
	110	115	114	65	84	95	10
	130	115	—	—	—	107	9
Group E. Low or Low Normal Cardiac Output; Normal Right Ventricular Pressures; Digitalized							
W. W., male, 46 years; B. S. A. 1.92; ASHD, EH, CS, MF, AF, IIB	Control	80, 60, 90, 80	110	75	92	28	2
			108	75	89		
	10*	95	134	97	111	27	1
	17	95	145	99	115	28	2
	33	100	126	86	103	26	1
	90	110	104	75	84	21	0
	120	100	112	77	83	22	1
D. P.,† male, 60 years; B. S. A. 1.91; ASHD, EH, CS, MF; old myocardial infarct; NSR, IIB	Control	83, 75, 75, 75	115	68	91	28	4
			122	72	94		
			118	68	90		
	27*	71	113	73	89	23	0
	54	75	128	63	97	25	1
	85	83	120	73	94	—	—
	117	88	113	71	94	29	0
	127	88	114	68	87	—	—
	142	88	120	73	96	31	4
	162	83	114	65	87	—	—

Continued on next page. All footnotes appear at end of table.

TABLE IV. THE EFFECT OF QUINIDINE ON HEART RATE AND BLOOD PRESSURES IN TWELVE PATIENTS WITH CARDIOVASCULAR DISEASE—(CONTINUED)

CASE	TIME (MIN.)	HEART RATE (PER MIN.)	BRACHIAL ARTERY (MM. HG)			RIGHT VENTRICLE (MM. HG)	
			SYSTOLIC	DIASTOLIC	MEAN	SYSTOLIC	DIASTOLIC
J. W., male, 64 years;	Control	71, 68, 65	110	61	82	27	4
B. S. A. 1.75;			107	62	82		
ASHD, ?HCVD,	60*	68	130	67	93	34	4
EH, CS, MF,	80	75	120	67	89	—	—
NSR, IIB	91	71	128	73	98	—	—
	113	75	118	67	89	31	6
	128	71	125	67	89	—	—
C. L., male, 57 years;	Control	70, 70, 80, 70	99	52	68	22	4
B. S. A. 1.72;			115	55	80		
Unk. HD, EH,			112	54	77		
AF, IIB	50*	80	117	58	84	23	4
	90	90	81	48	50	18	1
	115	90, 80	93	53	67	22	5
	120	90	87	51	66	—	—

*Time after quinidine administration.
†Femoral artery pressures during entire study.
‡Femoral artery pressures.

B. S. A. Body surface area in square meters.
ASHD Arteriosclerotic heart disease.
HCVD Hypertensive cardiovascular disease.
RHD Rheumatic heart disease.
Unk. HD Heart disease of unknown type.

AF Auricular fibrillation.
CI Cardiac insufficiency.
PND Paroxysmal nocturnal dyspnea.
NSR Normal sinus rhythm.
SA Sinus arrhythmia.
LBBB Left bundle branch block.

AI Aortic insufficiency.
CS Coronary sclerosis.
EH Enlarged heart.
MI Mitral insufficiency.
MF Myocardial fibrosis.
MS Mitral stenosis.

Pulm. F and E Pulmonary fibrosis and emphysema.

Group D: All four patients in this group demonstrated a fall in arterial systolic, diastolic, and mean pressures, although Patient H. C. with coarctation of the aorta showed only a minimal fall in both brachial and femoral artery pressures. In every instance the right ventricular systolic pressure fell, but the right ventricular diastolic pressure of only one patient (H. C.) was decreased. This patient also had the greatest fall in right ventricular systolic pressure (29 mm. of mercury).

Group E: One patient (C. L.) showed a fall, two (W. W. and J. W.), a rise, and one (D. P.), no change in arterial blood pressures. None of the four had any alterations in right ventricular pressures.

Of the twelve cardiac patients, irrespective of groups, eight showed a fall in arterial pressures, two showed no change, and two, a rise. Six of the eight also showed a fall in right ventricular systolic pressure; in only one of these did the

diastolic fall. Six patients showed no significant variations from the control values in the right ventricular pressures.

The fall in both arterial and right ventricular pressures was first seen as early as thirty minutes and as late as 145 minutes after ingestion of the drug. The fall in right ventricular pressures was associated in every instance with a fall in peripheral artery pressure. The rise in arterial blood pressure was noted as early as ten minutes after the administration of quinidine.

2. *The Effect of Quinidine on Heart Rate* (*Table IV*): The heart rate rose in five of the twelve patients (M. I., R. C., S. H., W. W., and C. L.), while in two patients (P. B. and H. I.) it fell, and in five (T. C., H. C., J. L., D. P., and J. W.), did not vary significantly. Three (H. C., J. L., and T. C.) of the eight patients who had falls in arterial blood pressure showed no change in heart rate, three (S. H., R. C., and C. L.) showed a rise, and two (P. B. and H. I.), a fall. One of the two subjects (D. P.) who had no change in arterial blood pressure had no significant alteration in heart rate, while the heart rate of the other (M. I.) rose. One (W. W.) of the patients with a rise in arterial blood pressure also had a rise in heart rate, while the heart rate of the other (J. W.) did not vary.

3. *The Effect of Quinidine on Cardiac Output* (*Table V*):

Group A: The two patients in this group demonstrated no change in cardiac output. A fall in arterial blood pressure was seen in one (R. C.).

Group B: In this one patient a fall in arterial and right ventricular pressures was accompanied by a fall of 19.2 per cent in cardiac output without change in heart rate.

Group C: The patient in this group had an increase of 18 per cent in cardiac output occurring simultaneously with the maximum fall in arterial and right ventricular pressures. At that time his heart rate had not changed significantly.

Group D: Three patients in this group showed a rise in cardiac output (20.7 37.1, and 30.4 per cent) associated with falls in arterial and ventricular blood pressures. The one patient (H. I.) who showed no significant alteration in cardiac output unfortunately did not have a cardiac output determination at the time of his fall in arterial blood pressure. None of these patients showed any real variation in heart rate.

Group E: The cardiac output of two of these patients (J. W. and C. L.) rose considerably (40.4 and 62.3 per cent, respectively), while the other two patients showed no change. In one patient (C. L.) the increase in cardiac output was associated with a fall in arterial blood pressure, no change in right ventricular pressures, and a slight rise in heart rate. The other patient (J. W.) had a slight rise in arterial blood pressure but no change in heart rate.

4. *The Effect of Quinidine on Peripheral Resistance* (*Table V*):

Group A: Only one (R. C.) of the two patients was examined for changes in peripheral resistance. Simultaneously with a fall in arterial blood pressure

the peripheral resistance fell 36 per cent and there was no change in cardiac output. Heart rate increased at the time of maximum hemodynamic changes.

Group B: A significant fall in blood pressure and in cardiac output occurred in Patient P. B. without any real change in peripheral resistance. The heart rate fell slightly.

Group C: Patient S. H. demonstrated a fall in arterial and right heart pressures associated with a rise in cardiac output and a 40 per cent fall in peripheral resistance. The heart rate did not increase until some time after the major changes in the circulation had taken place.

Group D: All four patients in this group followed the same pattern of response to quinidine. In each patient there was a considerable fall in arterial blood pressure, with the exception of H. C. in whom coarctation of the aorta may have added a barrier to arterial blood pressure change. In all four patients the right ventricular pressures fell quite markedly. In the case of Patient H. C., this fall was very large. In the three subjects (H. C., J. L., and T. C.) in whom cardiac output was measured at the time of the blood pressure fall, all three clearly showed a marked rise in cardiac output and a fall in peripheral resistance of −25, −50, and −35.7 per cent, respectively. The smallest fall in peripheral resistance was in the case of coarctation.

Group E: The patient (C. L.) whose arterial blood pressure fell showed a rise in cardiac output, no right ventricular pressure change, and a slight increase in heart rate. It was of interest in this case that the fall in peripheral resistance and the rise in cardiac output appeared some time before the fall in arterial blood pressure. Patient J. W. had a rise in cardiac output and a fall in peripheral resistance, but a rise in arterial blood pressure. The other two patients (W. W. and D. P.) showed no change in peripheral resistance.

5. *The Effect of Quinidine on Blood Volume* (*Table V*): Ten patients were studied for changes in total blood and plasma volume. Five patients showed an increase (6.7 to 13.9 per cent) in total blood volume, two, a decrease of 9 and 11 per cent, and four showed no change.

Discussion of Circulatory Changes Produced by Quinidine in Patients With Cardiovascular Disease: While there was no uniform effect of quinidine on the circulation in patients with cardiovascular disease, there occurred in most a significant lowering of arterial blood pressure. Eight of the twelve patients showed this change. This corresponds with the similar effect in four of the eight normal subjects.

In the normal subjects, as has been indicated, the fact that the arterial blood pressures tended to fall, while there was no change in right ventricular pressures or in cardiac output, suggests that this action of quinidine was largely or wholly peripheral: a vasodilatation of systemic arterioles.

In the patients with cardiovascular disease the total effects of quinidine were more extensive, though they varied in the different physiologic groups.

The two patients in Group A whose hearts were clinically not decompensated but showed some right ventricular systolic or diastolic hypertension

TABLE V. THE EFFECT OF QUINIDINE ON CARDIAC OUTPUT, PERIPHERAL RESISTANCE, AND BLOOD VOLUME IN TWELVE PATIENTS WITH CARDIOVASCULAR DISEASE

CASE	TIME (MIN.)	CARDIAC INDEX (L/MIN./SQ. M.)	OXYGEN CONSUMPTION (C.C./MIN.)	A-V O_2 DIFF. (VOL. %)	PERIPHERAL RESISTANCE (DYNES, SEC., CM^{-5})	BLOOD VOLUME TOTAL (C.C.)	BLOOD VOLUME PLASMA (C.C.)
Group A. Normal Cardiac Output; Elevated Right Ventricular Pressures							
M. I., female, 23 years; B. S. A. 1.71; interventricular septal defect; NSR, IA	Control	2.60‡	236	5.3	—	—	—
	65*	2.47	207	4.9	—	—	—
	112	2.31	213	5.4	—	—	—
R. C., male, 14 years; B. S. A. 1.66; RHD, EH, MS, MI, AI, SA; incomplete A-V block, IA	Control	3.02	145	3.1	1470	4320	2700
	125*	3.10	170	3.3	930	4825	3020
Group B. High Cardiac Output; Elevated Right Ventricular Pressures							
P. B., male, 55 years; B.S.A. 1.72; Unk. HD, EH, NSR, IA; ? cor pulmonale	Control	4.75	286	3.5	1080	5725	3490
	57*	3.83	264	4.1	1033	—	—
	119	4.00	275†	4.0	1110	—	—
	149	—	—	—	—	5720	3200
Group C. Low Cardiac Output; Elevated Right Ventricular Pressures; No Digitalis							
S. H., male, 57 years; B.S.A. 1.50; HCVD, ASHD, EH, CS, MF, NSR, CI, PND, LBBB, IIIC	Control	2.03	174	5.7	3530	4360	2640
	42*	1.86	139	5.0	2910	—	—
	82	2.40	187	5.2	2110	—	—
	107	—	—	—	—	4650	2800
Group D. Low or Normal Cardiac Output; Elevated Right Ventricular Pressures; Digitalized							
H. I., male, 51 years; B.S.A. 1.70; HCVD, EH, NSR, CI, IIIC; arteriolar nephrosclerosis	Control	2.77	283	6.0	2630	5460	3050
	60*	2.64	269	6.0	2600	—	—
	127	2.84	290	6.0	2480	6220	3820
H. C., male, 45 years; B.S.A. 1.85; coarctation of the aorta; EH, NSR, PND, CI, IIIC	Control	2.76	250	4.9	2280 1570§	6000	3845
	58*	2.71	280	5.6	2460	—	—
	133	3.49	309	4.8	1700 1165§	—	—
	156	—	—	—	—	5330	3465

TABLE V. THE EFFECT OF QUINIDINE ON CARDIAC OUTPUT, PERIPHERAL RESISTANCE, AND BLOOD VOLUME IN TWELVE PATIENTS WITH CARDIOVASCULAR DISEASE—(CONTINUED)

CASE	TIME (MIN.)	CARDIAC INDEX (L/MIN./SQ. M.)	OXYGEN CONSUMPTION (C.C./MIN.)	A V O_2 DIFF. (VOL. %)	PERIPHERAL RESISTANCE (DYNES, SEC., CM^{-5})	BLOOD VOLUME TOTAL (C.C.)	BLOOD VOLUME PLASMA (C.C.)
J. L., male, 63 years; B.S.A. 1.43; RHD, EH, MS, MI, AI, NSR, CI, IIC	Control	2.05	173	5.9	2950	3995	2145
	62*	2.81	181	4.5	1470	—	—
	132	2.45	182	5.2	1880	4445	2440
T. C., male, 49 years; B.S.A. 1.62; cor pulmonale; EH, NSR, CI, IIC; Pulm. F and E	Control	3.18	345	6.7	1380	6740	2930
	55*	3.43	317	5.7	887	—	—
	110	4.15	316	4.7	1000	6130	2760
Group E. Low or Low Normal Cardiac Output; Normal Right Ventricular Pressures; Digitalized							
W. W., male, 46 years; B.S.A. 1.92; ASHD, EH, CS, MF, AF, IIB	Control	2.23	270	6.3	1705	6780	3030
	57*	2.13	274	6.7	—	—	—
	120	2.32	311	7.0	1482	7270	3270
D. P., male, 60 years; B.S.A. 1.91; ASHD, EH, CS, MF; old myocardial infarct; NSR, IIB	Control	1.59	213	7.0	2360	4970	1655
	54*	1.65	205	6.5	2450	—	—
	162	1.44	217	7.9	2530	4810	1595
J. W., male, 64 years; B.S.A. 1.75; ASHD, ?HCVD, EH, CS, MF, NSR, IIB	Control	2.77	252	5.2	1400	7250	4135
	60*	3.43	258	4.3	1285	—	—
	113	3.89	279	4.1	1035	6960	3895
C. L., male, 57 years; B.S.A. 1.72; Unk. HD, EH, AF, IIB	Control	1.68	275	9.5	1970	—	—
	50*	2.72	296	6.3	1008	—	—
	115	1.82	206	6.6	1690	8210	5000

*Time after quinidine administration.
†Assumed oxygen consumption (average of values obtained in first and second cardiac outputs).
‡Aortic flow and blood returning to the right auricle. Pulmonary flow, measured once, was somewhat larger because of the presence of the interventricular septal defect.
§Calculated on basis of femoral artery mean pressures.
B. S. A. = body surface area in square meters.

ASHD	Arteriosclerotic heart disease.
HCVD	Hypertensive cardiovascular disease.
RHD	Rheumatic heart disease.
Unk. HD	Heart disease of unknown type.
AI	Aortic insufficiency.
CS	Coronary sclerosis.
EH	Enlarged heart.
MI	Mitral insufficiency.
MF	Myocardial fibrosis.
MS	Mitral stenosis.
AF	Auricular fibrillation.
CI	Cardiac insufficiency.
PND	Paroxysmal nocturnal dyspnea.
NSR	Normal sinus rhythm.
SA	Sinus arrhythmia.
LBBB	Left bundle branch block.
Pulm. F and E	Pulmonary fibrosis and emphysema.

behaved like the normal subjects, one patient showing a fall in arterial pressure and the other not, but both having no change in right ventricular pressures nor in their (normal) values of cardiac output, as a result of quinidine. In the one patient showing a decreased arterial pressure, this effect was thus apparently a peripheral vasodilatation.

The patient in Group B with a high cardiac output and right-sided systolic hypertension, without clinical evidence of decompensation, showed a fall in arterial pressure, in the elevated right ventricular pressure, and in cardiac output, after quinidine. Presumably these pressure effects were chiefly due to vasodilatation. Some depressive action on the heart itself cannot be excluded. This was the only instance of this type of response.

Groups C and D, patients with initially low cardiac outputs, elevated right ventricular pressures, and, in addition, clinical signs of failure, showed significantly different reactions to quinidine from the patients whose cases have just been cited. Both the nondigitalized patient of Group C and the four digitalized patients of Group D had, after quinidine: (1) fall in arterial pressures, (2) fall in right ventricular systolic pressures, and (3) a considerable increase in cardiac output.

This series of events could be explained on the basis that the peripheral vasodilator effect of quinidine, in lowering arterial pressure, relieved the strain on the left heart, allowing it to empty more completely, with increased stroke volume; this, in turn, decreased pulmonary congestion and lowered right ventricular systolic pressure.

It is also possible, however, that quinidine may have produced the increase in cardiac output, in part, by a direct action on the heart in these cases.

There is some further evidence suggestive of a direct action of quinidine on the heart. Patient H. C., for example, had only a minimal fall in arterial pressure, but a large drop in right ventricular pressures and a large increase in cardiac output.

The results in Group E, while not very consistent, are also somewhat suggestive of a direct effect of quinidine on the heart. These individuals, as already noted, were patients with heart disease who had recovered clinical compensation at the time of study, and were classified II,B. In Patient C. L., with fall in arterial pressure and rise in cardiac output, the myocardial effect of quinidine is suggested by the fact that the increase in cardiac output took place before the arterial pressure fell. Patient J. W. had a 40 per cent increase in cardiac output, with a small rise in arterial blood pressure, again suggesting some myocardial action of the drug. In results as variable as those obtained in Group E, however, no definite conclusions can be drawn.

Variations in heart rate were not consistent in the cardiac cases and bore no constant relationship to any other circulatory changes. Blood volume changes were few and not correlated with other effects. It seems not unlikely that in the three hours of the study there may have been enough small fluctuations in body fluids to produce occasional irregular changes in blood volume.

In summary, the chief dynamic effect of a single dose of quinidine in subjects with normal circulations was a fall in arterial blood pressure which occurred in

about one-half of the cases, while in patients in clinical congestive heart failure, a fall in arterial blood pressure was usually combined with a drop in a previously elevated right ventricular systolic pressure and an increase in a previously low cardiac output.

It is hardly possible to apply these physiologic and pharmacologic data on the effects of a single dose of quinidine to the clinical use of the drug. It may be that the effects described are a part of its therapeutic action, especially the combined effects seen in the heart failure cases. If such is the case, the mechanism is as yet obscure. It seems fairly clear that quinidine action is fundamentally different from digitalis action, since the increased cardiac output is not associated with a fall in diastolic filling pressure as measured by right ventricular diastolic pressure.[32] Further work will be needed to decide this problem.

So far as the vasodilator action of quinidine is concerned, it is quite possible that in susceptible subjects this becomes an unfavorable effect. Routine examination of the blood pressure during quinidine therapy may settle this question.

C. *Electrocardiographic Changes Produced by Quinidine.*—Electrocardiographic changes were noted in all eight normal subjects and were of two types. In seven subjects there was a consistent decrease in amplitude of the T waves in standard Leads I and II, and occasionally in Lead III. In the eighth subject, T-wave changes were difficult to evaluate for technical reasons. The T-wave changes appeared as early as thirty minutes and as late as ninety-five minutes after quinidine. The second electrocardiographic abnormality produced was a prolongation of the Q-T interval to abnormal length in all eight normal subjects. This occurred as early as twenty-four minutes and as late as eighty-eight minutes after administration of the drug. In three subjects the Q-T interval change occurred before the T waves altered; in two the decrease in T-wave amplitude was noted first; and in two the changes occurred simultaneously. There was no change in P waves, P-R interval, or QRS duration.

Ten cardiac patients also showed electrocardiographic changes of the two types mentioned. The tracings in two patients with auricular fibrillation (W. W. and C. L.) could not be analyzed satisfactorily for either T-wave or Q-T interval changes. Eight of the ten cardiac patients had T-wave changes, which were noted as early as twenty-six minutes and as late as 160 minutes after quinidine. One patient's changes were equivocal and in the other patient's tracings the markedly prolonged Q-T interval made T-wave measurements difficult. The prolongation of the Q-T interval, noted in all ten cardiac patients, first appeared at thirty minutes in one patient and at 125 minutes in another. Three patients had T-wave changes appear before Q-T interval prolongation, while two had the changes appear in reverse order. In four patients the changes were simultaneous. In one patient (R. C.) with a prolonged P-R interval (0.24 second), the conduction time returned to normal (0.20 second) 115 minutes after the drug was given. Four of the cardiac patients developed a right bundle branch block pattern fifty-three to eighty-four minutes after administration of the drug. One patient with left bundle branch block and a QRS of 0.12 second was found to have a QRS of 0.14 second, 107 minutes after quinidine.

There was no significant alteration in the relationship of mechanical to electrical events[33] in the cardiac patients, with the exception of those in whom right bundle branch block appeared. In these patients the ventricular asynchronism typical of this abnormality became apparent.

The changes in the electrocardiograms of normal and cardiac subjects were interpreted as indicative of an effect of the drug on the myocardium. Since these changes appeared in all normal subjects and ten of the twelve cardiac patients, it can be stated that the drug reached the cardiac muscle. In the two patients with auricular fibrillation where no electrocardiographic effect of the drug could be noted, one (C. L.) had definite hemodynamic effects attributable to the drug and the other (W. W.) did not.

The electrocardiographic changes provide strong evidence that there is some central or myocardial action of quinidine.

D. *Ward Study.*—A supplementary study of the effect of quinidine on blood pressure alone was carried out on patients on the wards (Fig. 1). This

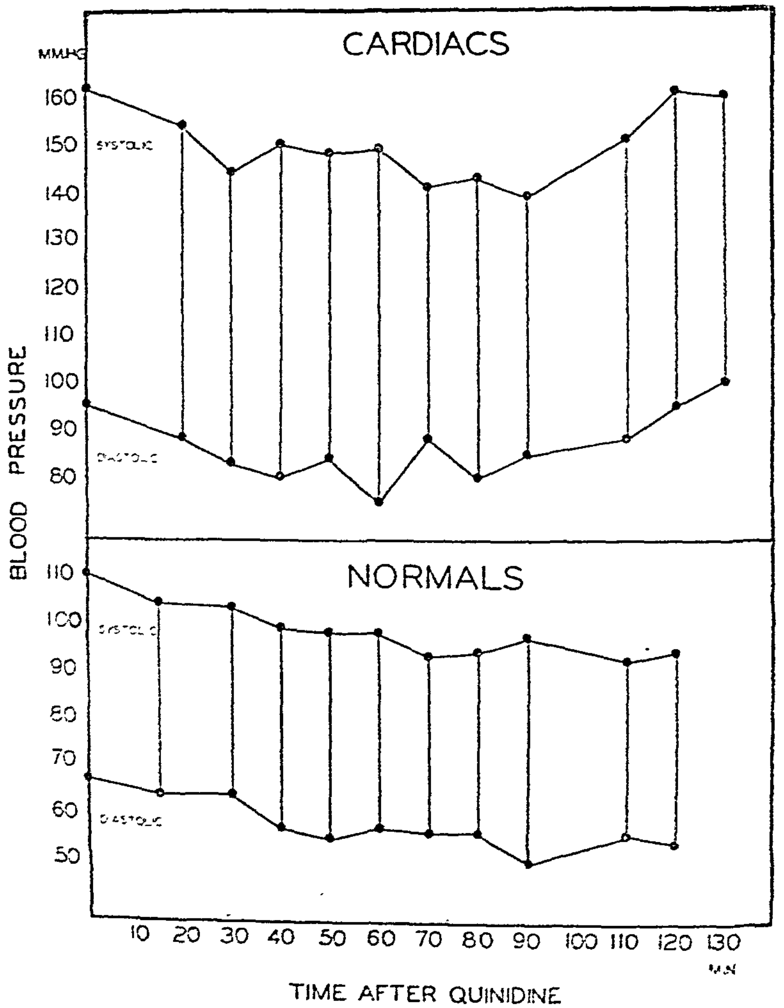

Fig. 1.—The average effect of quinidine on arterial blood pressure in eleven cardiac patients and ten normal subjects.

Blood pressure was recorded by sphygmomanometer. Note the significant drop in both groups which averaged nearly 20 mm. Hg in both systolic and diastolic pressures.

was done to confirm the unexpected blood pressure fall and to exclude the effects of sedation and the catheterization technique. Ten patients with essentially normal circulation and eleven patients with cardiovascular disease received 0.8 Gm. quinidine sulfate by mouth. These patients had been fasting and in bed for twelve hours and they had received no sedation for the twelve hours prior to the observation period. In the majority of patients three control blood pressure determinations, taken by sphygmomanometer, were obtained during the first half hour of the study. The range of variation for both systolic and diastolic pressures was computed from these control values and was found to be plus or minus 10 mm. Hg for both normal subjects and cardiac patients. In some instances wide fluctuations in diastolic pressures made any evaluation of a change impossible. Of the ten normal subjects, seven showed a definite fall in both systolic and diastolic pressures. The maximum changes were a fall of 61 mm. Hg systolic and 33 mm. Hg diastolic. Of the eleven cardiac patients, ten showed an unequivocal fall in both systolic and diastolic arterial blood pressures, and the greatest fall for each was 53 and 34 mm. Hg, respectively. One of these ten showed an early rise in blood pressure preceding the fall. One patient showed only a rise in blood pressure, but this patient was extremely restless throughout the study. In both normal subjects and patients with cardiovascular disease, the initial fall in blood pressure was recorded as early as fourteen minutes and as late as 123 minutes after administration of quinidine.

The average systolic and diastolic blood pressures of the ten normal subjects and eleven patients with cardiovascular disease are plotted in Fig. 1. Each point represents the average systolic or diastolic blood pressure of each group at the time indicated.

Note on Side Effects of Quinidine.—The dosage used (0.8 Gm.) produced gastrointestinal symptoms in only two (R. K. and A. S.) of the forty-one patients studied. These symptoms consisted of nausea, epigastric pain, and lower abdominal cramps and were associated with a fall in arterial blood pressure in both patients. No other side effects of the drug were encountered.

SUMMARY AND CONCLUSIONS

The effect of 0.8 Gm. of oral quinidine sulfate on the heart and circulation was studied in forty-one subjects. In twenty patients an extensive investigation of the circulatory hemodynamics was carried out by means of the right heart catheterization technique. Clinical investigation of the blood pressure alone was undertaken in twenty-one subjects.

1. A fall in arterial blood pressure was found in twelve of the eighteen normal subjects, an incidence of 66.7 per cent. The results obtained in five of these twelve patients indicate that the fall in arterial blood pressure was unaccompanied by any change in cardiac output or right ventricular pressure.

2. Eighteen of the twenty-three patients with cardiovascular disease showed a fall in arterial blood pressure, an incidence of 78.3 per cent. It was apparent, however, that in these cardiac patients the subsequent readjustments

in the circulation were dependent upon the physiologic status of the patient. In patients with normal cardiac output, no change in this determination was measurable. Patients with low cardiac outputs and elevated right ventricular systolic pressures responded with a shift toward more normal values.

3. It is suggested tentatively that the fall in arterial blood pressure following quinidine is due in large measure to peripheral vasodilatation. Some evidence for an effect on the myocardium is also presented.

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II. CORRELATION OF ELECTROCARDIOGRAPHIC AND PATHOLOGIC FINDINGS IN LARGE ANTEROLATERAL INFARCTS

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OBSTRUCTION to the flow of blood through the anterior descending coronary artery and its branches characteristically produces a large infarct of the apical one-third to two-thirds of the anterior wall of the left ventricle which almost invariably extends into the septum, usually into the apical one-third to one-half of the lateral wall, often into the apical one-third of the posterior aspect of the left ventricle, but seldom crosses over into the right ventricle.[1-3] In animals with infarcts of this type, produced by ligation of the anterior descending branch of the left coronary artery, Wilson and associates[4,5] accurately localized the position of the lesion through multiple epicardial leads. The findings in multiple precordial and unipolar limb leads have been described for large anterior infarcts in human subjects,[6-9] but have been carefully correlated with those at autopsy in only a few cases.[6,10,11]

A study, therefore, has been undertaken to determine the accuracy and limitations of multiple precordial and unipolar limb leads in the detection of extensions of large anterior infarcts into the lateral and posterior walls of the left ventricle, into the septum, and into the right ventricle, and their dependability for the estimation of the distribution of the infarct between the endocardial and epicardial surfaces of the underlying wall. The methods of electrocardiographic and pathologic study have been described.[12] In a series of 161 cases in which multiple precordial and limb leads were taken during life and in which myocardial infarction was accurately localized at autopsy, there were sixty-four patients with a large anterior infarct which extended into other portions of the left ventricle. The infarct continued into the apical one-third or more of the lateral wall in fifty-seven cases, extended into the septum in fifty-nine, crossed over into the anterior wall of the right ventricle in five cases, and extended through the septum or around the tip of the left ventricle to involve the apical one-third or more of the posterior wall in thirty-seven cases. The electrocardiographic findings have been analyzed in detail for each case and have been correlated with the area of involvement of the anterior, lateral, and posterior walls of the left ventricle, the septum, and the right ventricle, with the distribution of the lesion between endocardium and epicardium, and with a pathologic estimate of the age of the infarct.

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To exemplify and summarize the correlation between the electrocardiographic findings and the various ramifications of the infarct at autopsy, the cases have been classified into three groups, which will be considered in separate reports. This manuscript comprises a detailed analysis of thirty cases, which collectively illustrate the various electrocardiographic patterns associated with infarction of the apical portion of the anterior and lateral walls of the left ventricle, and includes a summary, correlating the electrocardiographic and pathologic findings in all fifty-seven cases with a large anterior infarct extending into the apical one-third or more of the lateral wall. In the next communication, a similar analysis will be made of eighteen cases of coexistent anteroposterior infarction and a summary will be given of all thirty-seven cases in which the anterior infarct extended through the septum or around the tip of the left ventricle to the apical one-third or more of the posterior aspect. In the next report nineteen cases of infarction of the interventricular septum will be analyzed, and the findings in all cases in which a large anterior infarct extended into the septum or right ventricle will be summarized.

CASE REPORTS

CASE 21.—A man, 69 years of age, was well until November, 1943, when he began to have paroxysmal nocturnal dyspnea. Congestive failure supervened, leading to hospital admission on Dec. 19, 1943. No clinical evidence of myocardial infarction was found during his hospital stay. In the spring of 1944 he began to have brief attacks of stabbing precordial pain. Following an exceptionally severe attack in August, 1944, decompensation recurred and led to hospitalization elsewhere. Late in October, another attack of prolonged stabbing precordial pain occurred, followed by cardiac failure and readmission on October 30. Orthopnea persisted in spite of therapy and bronchopneumonia developed, ending in death on the twelfth hospital day.

Electrocardiographic Findings.—Electrocardiograms obtained during his three admissions are reproduced in Fig. 1. The tracing of Dec. 23, 1943, was taken after the administration of a total of 1.5 Gm. digitalis during the three preceding days. The tall R wave and slightly delayed intrinsicoid deflection in Leads V_4 and V_6 were typical of left ventricular hypertrophy. The RS-T segment and T wave exhibited evidence of full digitalis effect. Maintenance doses of 0.1 Gm., daily, were continued for the rest of his life. The electrocardiogram of September 28 was taken about one month after the first attack of prolonged precordial pain. The last two tracings were obtained after the second attack. The pattern in Lead V_2 was practically constant throughout and was characterized by a small R, a deep S, an elevated RS-T junction, and upright T wave consistent with the changes produced by left ventricular hypertrophy in leads from the right side of the precordium. The replacement of the tall R originally present in Lead V_4 by a QS complex was diagnostic of infarction of the apical portion of the anteroseptal wall of the left ventricle, particularly in view of the persistence of the initial R in Lead V_2. Attention is directed to the presence of a distinct notch on both limbs of the QS complex of Lead V_4 on September 28, to the disappearance of the final notch in the tracing of October 31, and to the absence of both notches on November 6. The notches were probably due to activation of islands of responsive muscle in the infarcted anterior wall, and their disappearance after the second attack suggested reinfarction in the same area. A QS pattern of central zonal type was also present in Lead V_3 of the final tracing. Lead V_6 of the second and fourth tracings displayed a Q wave of 2.0 mm., which was 25 to 33 per cent of the amplitude of the succeeding R wave. This pattern, taken in conjunction with the fact that the R wave had undergone a 66 per cent reduction in voltage since December, 1943, was construed as evidence of extension of the infarct into the subendocardial portion of the lateral wall of the left ventricle. The changes in Leads aV_L and I were roughly parallel to those in V_6. A more typical marginal pattern was recorded in Lead V_5, which exhibited

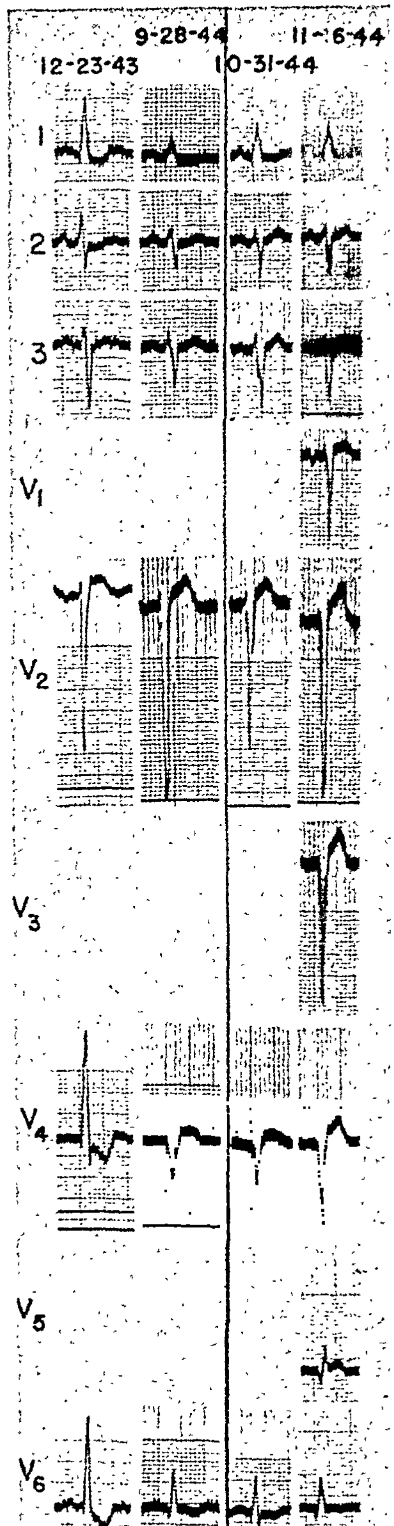

Fig. 1.—Serial electrocardiograms of Case 21 before and after development of anterolateral infarction.

a broad Q wave, 2.5 mm. in depth, followed by a slurred R, 5.0 mm. tall, an elevated RS-T junction, and monophasic, upright T wave, suggestive of the injury phase of reinfarction.

Pathologic Findings.—The heart weighed 720 grams and exhibited marked left ventricular hypertrophy and moderate secondary right ventricular hypertrophy. A large organized infarct of at least two months' duration was found in the anterolateral wall, as outlined in Fig. 2. Although the infarct extended through the entire wall, the subepicardial portion was somewhat patchy in the third and fourth segments. There was definite evidence of recent reinfarction of the lateral portion of the apex. The location and age of the infarct corresponded closely to that predicted from the serial electrocardiograms.

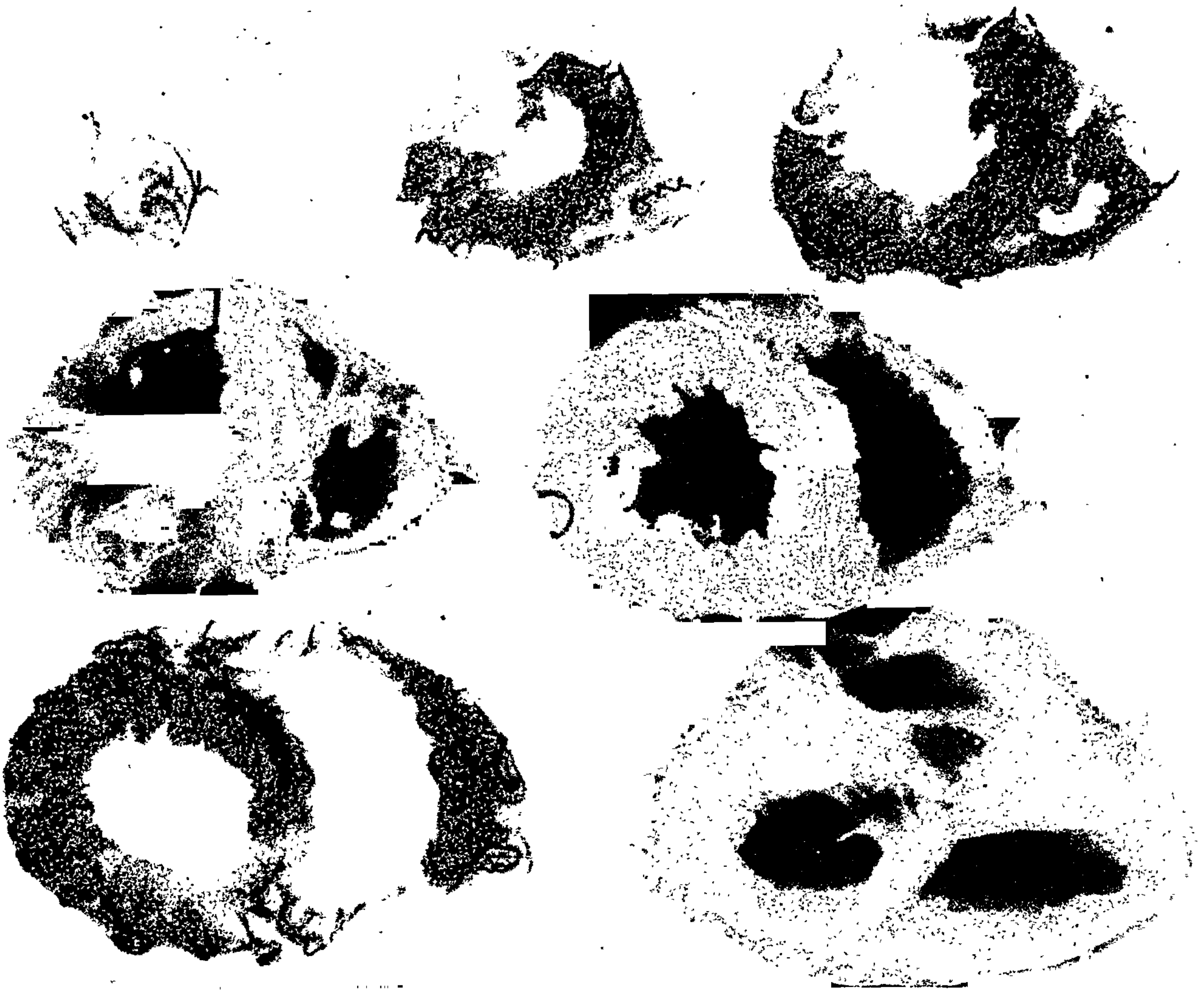

Fig. 2.—Roentgenogram of the injected heart of Case 21.

CASE 22.—A man, 49 years of age, had had cough, hemoptysis, dyspnea, and right-sided pleural pain for two weeks, but gave no definite history of myocardial infarction. Physical examination revealed bronchopneumonia, left ventricular hypertrophy, and a blood pressure of 220/110. Patient died suddenly on the tenth hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained one hour after hospital admission and before the administration of digitalis is reproduced in Fig. 3,*A*. A definite R wave was present in Lead V_1, a minute R was barely detectable in V_2, and a QS complex was present in Leads V_3, V_4, and V_5. Lead V_6 displayed an initial Q, which was about 20 per cent of the suc-

ceeding R wave, whereas Lead aV_L showed a Q of 3.0 mm. and an R of 26 millimeters. The QS complex in Leads V_3, V_4, and V_5 was indicative of a transmural infarct of the anteroseptal and anterolateral aspects of the apex, and the marked RS-T elevation in these leads pointed to a very recent lesion. The standard leads showed evidence of left ventricular hypertrophy, but were not diagnostic of recent infarction. Two subsequent tracings, taken on the sixth and eighth hospital days, showed the usual evolution in T waves, but no significant change in QRS.

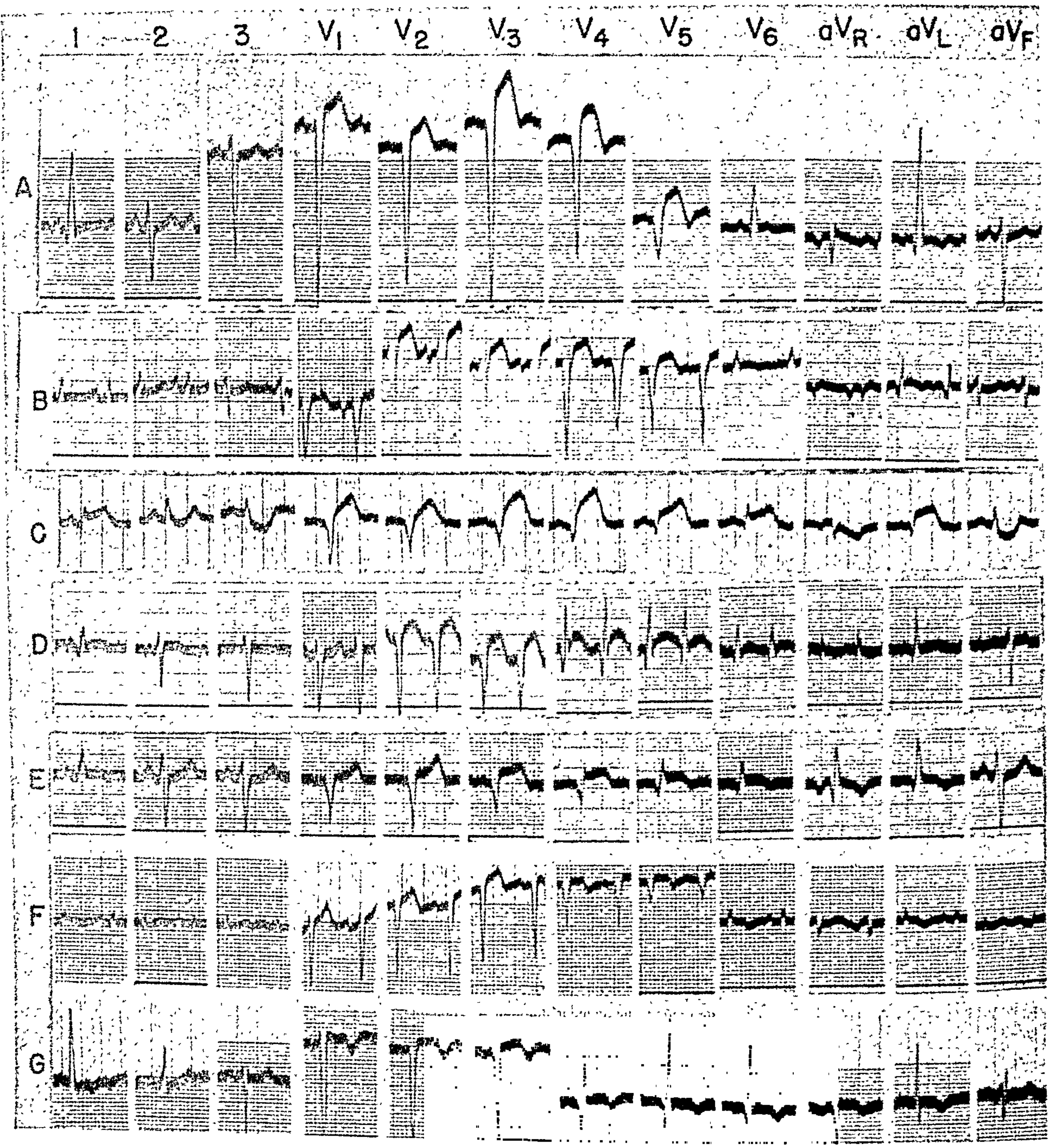

Fig. 3.—Recent anterolateral infarction. *A*, Case 22; *B*, Case 23; *C*, Case 24; *D*, Case 28; *E*, Case 29; *F*, Case 31; *G*, Case 33.

Pathologic Findings.—The heart weighed 721 grams and exhibited marked left ventricular hypertrophy. A recent infarct involved the entire apical one-third of the anterolateral wall of the left ventricle and septum and extended a little higher in the subendocardial one-half of the anterior wall, as outlined in Fig. 4. Death was due to rupture of the anterior wall just above the apex. Although a QS pattern would have been expected in association with the transmural infarction, the noteworthy feature of this case was the consistent finding of a QS in three precordial leads (V_3, V_4, and V_5), resulting from a relatively small area of transmural infarction confined to the apical one-third of the left ventricle. The lack of electrocardiographic signs of septal infarction may have been due to limitation of the lesion to the apical one-third. The failure of Lead aV_F to show signs of infarction of the posteroapical portion of the left ventricle was attributable to horizontal position with subdiaphragmatic transmission of potential variations of the posterior inferior surface of the right rather than those of the left ventricle.

CASE 23.—A previously healthy man, 64 years of age, had had several transient attacks of retrosternal pain during the preceding fortnight, and on the night of admission to the hospital was awakened by a much more severe and prolonged attack. Hospital course was uneventful until the twelfth day, when he died during sleep.

Electrocardiographic Findings.—An electrocardiogram obtained twelve hours after the onset of the protracted retrosternal pain is reproduced in Fig. 3,*B*. The prominent intrinsicoid deflection and diphasic contour of the P waves in Leads V_1 and V_2 suggested that the electrode was in the vicinity of the right atrium and indicated that the ventricular complex in these leads reflected principally the potential variations of the right side of the septum and the right ventricle. Attention is directed to the presence of an initial R wave in Leads V_1 and V_2, to the decrease in its amplitude in V_3, to the QS complex of central zonal type in V_4 and V_5, and to the abnormal QR of marginal zonal type in Leads V_6 and aV_L. These findings were indicative of infarction of the anterior and lateral wall of the apical portion of the left ventricle. The elevation of the RS-T junction, straightening of the segment, and monophasic, upright T wave in all precordial leads and in Lead aV_L pointed to a recent infarct in the stage of injury. It is noteworthy that a definitely abnormal Q wave was present in Lead aV_L, but was cancelled out in Lead I because of an equivalent initial negativity of the right arm.[13] The standard leads showed a slurred QRS of low voltage, but were not diagnostic of infarction.

Pathologic Findings.—The heart weighed 571 grams as a result of left ventricular hypertrophy. A very large, recent transmural infarct covering the entire anterior wall of the left ventricle, extending into the lateral portion of the apex, and involving the entire septum in the apical two segments and the anterior one-half in the remainder, was clearly outlined in the roentgenogram reproduced in Fig. 5. The involvement of the anteroseptal and anterolateral aspect of the apex was adequately represented by the QS in Leads V_4 and V_5 and the abnormal QR of Leads V_6 and aV_L. The infarction of the septum and adjacent anteroseptal wall was suggested by the RS-T displacement in Leads V_1, V_2, and V_3, but was so extensive that it should have given rise to bundle branch block, or at least to abnormal QS deflections in the first three precordial leads. Because of the short interval between the onset of the attack and the recording of the electrocardiogram, it is possible that degenerative changes had not progressed sufficiently in the septum and basal two-thirds of the anteroseptal wall to obliterate their response to the activating impulse. It is also possible that the original infarct was more like that in Case 22 (Fig. 4), and that extension into the base of the anterior wall and septum took place during the twelve-day interval before death. Since no subsequent tracings were obtained, the explanation for the discrepancy between electrocardiographic and pathologic findings is left unsettled. If, at the time of the electrocardiogram, the infarct had attained the size demonstrated at autopsy, the R waves in Leads V_1, V_2, and V_3 may have been contributed by activation of the outer wall of the right ventricle. A small, completely healed posterior infarct was also found at autopsy, as indicated by the broken lines in Fig. 5, but was not detected electrocardiographically, perhaps because the heart was in horizontal position.

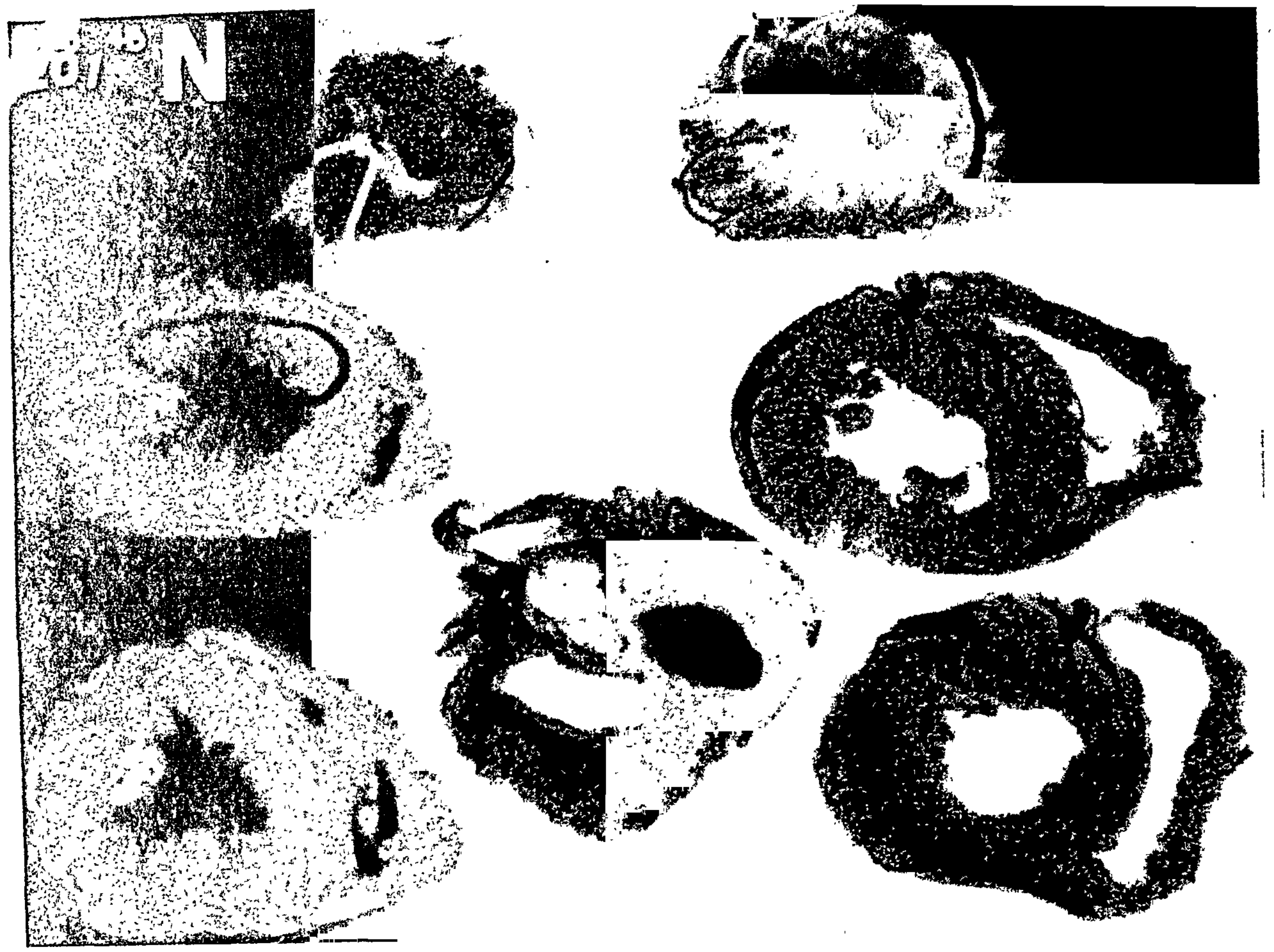

Fig. 4.—Roentgenogram of the injected heart of Case 22.

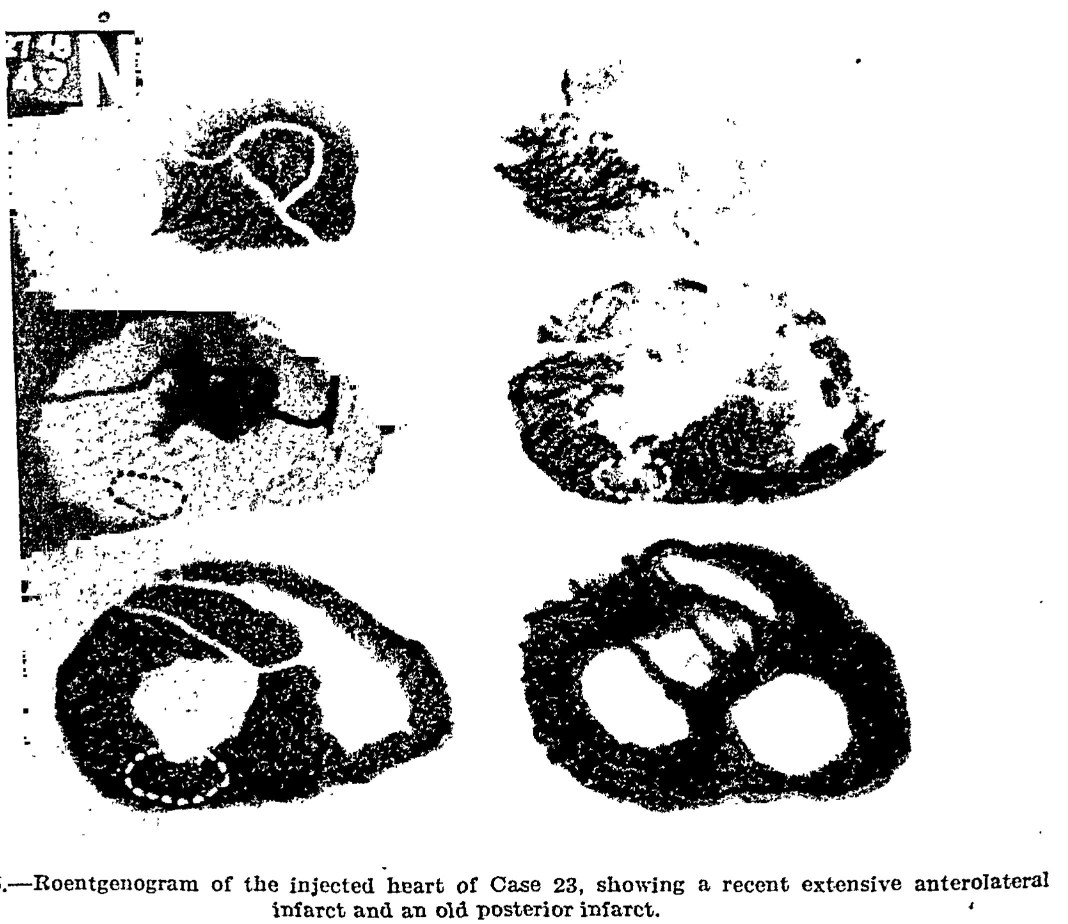

Fig. 5.—Roentgenogram of the injected heart of Case 23, showing a recent extensive anterolateral infarct and an old posterior infarct.

CASE 24.—A woman, 54 years of age, had had angina pectoris for five years and was admitted to the hospital because of a very severe attack of oppressive retrosternal pain of five and one-half hours' duration. The patient remained in circulatory collapse and expired fifty-four hours later. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained ten hours after the onset of the present illness is reproduced in Fig. 3,*C*. From the presence of a QS complex, markedly elevated RS-T junction, and monophasic, upright T wave in Leads V_1, V_2, V_3, V_4, V_5, and aV_L, and an abnormal QR complex and elevated RS-T junction in V_6, a diagnosis was made of a large, recent infarct, involving the anterior and lateral walls of the left ventricle and extending into the septum. The pattern in Lead aV_L was carried over into Lead I, so that a diagnosis of anterolateral infarction could readily be made from the standard leads. There was marked reciprocal depression of the RS-T junction in Leads aV_F and III.

Pathologic Findings.—The heart weighed 300 grams and displayed a rupture in the anterior wall with hemopericardium. A recent transmural infarct was found, involving almost the entire anterior wall and extending into the septum and lateral aspect of the apex, comparable to that in Case 23 (Fig. 5). There was good correlation between the electrocardiographic findings and the extensive infarct of the anterolateral wall of the left ventricle. The absence of the R wave in Leads V_1 and V_2 was probably a manifestation of the septal involvement.

CASE 25.—A woman, 51 years of age, with diabetes, began to have attacks of prolonged retrosternal oppressive pain four days before hospital admission. She was brought to the hospital in circulatory collapse and died the following day.

Electrocardiographic Findings.—Electrocardiograms were obtained on the first and second hospital days, but are not reproduced because of the striking similarity of the QRS-T pattern to that in Case 24 (Fig. 3,*C*). Auricular tachycardia with a rate of 165 per minute was found in both tracings; a 1 : 1 ventricular response was present in the first and complete auriculoventricular block in the second tracing. A diagnosis of a large, recent infarct of the anterolateral wall of the left ventricle was made. Extension into the septum was postulated to account for the QS pattern in leads over the right ventricle and for the terminal auriculoventricular block.

Pathologic Findings.—The heart weighed 495 grams and showed a recent transmural infarct similar in extent and distribution to that in Case 23 (Fig. 5). There was no evidence of atrial infarction. The terminal auriculoventricular block might have been related to the extensive septal infarction. The QRS-T pattern in the precordial and limb leads corresponded closely with the location of the infarct in the septum and anterior and lateral walls of the left ventricle.

CASE 26.—A man, 48 years of age, who had had no previous cardiovascular symptoms, was seized with a vise-like retrosternal pain and was hospitalized one and one-half hours later. The blood pressure was 220/150. Death occurred eight hours after the onset of the retrosternal pain.

Electrocardiographic Findings.—An electrocardiogram was obtained three hours after the onset of the pain, but is not reproduced because of its close resemblance to that in Case 24 (Fig. 3,*C*). A QS complex of the central zonal type, markedly elevated RS-T junction, and monophasic, upright T wave were present in all six precordial leads and in aV_L and led to a diagnosis of very large, recent infarct of the anterior and lateral wall of the left ventricle extending into the septum.

Pathologic Findings.—The heart weighed 596 grams and showed a rupture of the anteroapical wall with hemopericardium. There was a very large, recent transmural infarct, which involved the anterior wall and septum, as in Case 23 (Fig. 5), but extended around the entire circumference of the left ventricle in the two apical segments. The findings in the six precordial leads and in aV_L corresponded closely with the transmural infarction of the anterior and lateral walls of the left ventricle. Infarction of the septum was considered responsible for the QS complex and RS-T elevation in Leads V_1 and V_2, but did not cause prolongation of the QRS interval. The involvement of the posterior portion of the apex was not revealed by Lead aV_F or by Leads II and III.

CASE 27.—A man, 59 years of age, gave a history of one attack of transient retrosternal oppression one month previously and a second, much more prolonged attack of more severe pain on the evening of hospital admission. Death occurred on the fourth hospital day.

Electrocardiographic Findings.—An electrocardiogram is not reproduced because of its resemblance to that in Case 23 (Fig. 3,*B*), except in Leads V_2 and V_3, where it exhibited a QS rather than an RS complex. The findings were typical of a large, recent infarct of the anterior and lateral walls of the left ventricle.

Pathologic Findings.—The heart weighed 465 grams and exhibited a very large recent infarct, almost identical in location with that in Case 26. Although transmural infarction of the lateral wall was found in the apical two segments in both cases, a QS pattern was recorded in Leads V_5, V_6, and aV_L in Case 26 and only in Lead V_5 in this case. The difference may have been due to differences in cardiac position. The heart in Case 26 was moderately rotated in a clockwise direction, which would favor transmission of the potential variations of the large anterior portion of the infarct toward the axilla, whereas the heart in the present case was rotated counterclockwise, which would facilitate transmission of the potential variations of the uninfarcted portion of the lateral wall into the axilla, thus accounting for the upright portion of the abnormal QR complex in Leads V_6 and aV_L. The horizontal position of the heart in this case probably accounted for the absence of signs of the posteroapical infarct in Lead aV_F.

CASE 28.—A man, 63 years of age, was admitted with a history of a productive cough of four months' duration and a 50-pound weight loss referable to bronchiogenic carcinoma. During the second hospital week, auricular fibrillation developed and dyspnea increased, but no definite history of constrictive pain could be elicited. Death occurred on the twenty-fourth hospital day.

Electrocardiographic Findings.—An electrocardiogram taken on the sixteenth day, after the administration of 2.8 Gm. digitalis during the preceding week, is reproduced in Fig. 3,*D*. A previous tracing taken three days earlier had shown auricular fibrillation and a similar QRS-T pattern. Sinus rhythm with abnormal diphasic P waves was present on the sixteenth day, when the standard leads were recorded, and auricular fibrillation recurred just before the precordial leads were taken. A 3.0 mm. R wave, an isoelectric RS-T junction, and normal, upright T wave were recorded in Lead V_1 and contrasted sharply with the abnormalities in the remaining leads. A QS deflection was found in Leads V_2 and V_3 and a QR complex with an abnormally deep Q was evident in Leads V_4, V_5, and V_6. The QRS changes were indicative of a large, transmural anterior infarct, which extended subendocardially into the lateral wall. On the basis of the displacement and typical domelike contour of the RS-T segment and monophasic, upright T wave, it was thought that the infarct was of recent origin, but too little attention was given to the absence of serial changes in three tracings taken over a period of ten days. Signs suggestive of a recent, anterolateral infarct were present in the standard leads.

Pathologic Findings.—Death was due to bronchiogenic carcinoma, which had metastasized to the right atrium and pericardial sac and had led to a generalized fibrinous pericarditis. The heart weighed 459 grams and exhibited an old, completely healed infarct of anterior and anterolateral walls of the left ventricle, occupying a position almost identical to that in Case 21 (Fig. 2). The dense part of the infarct was confined to the subendocardial one-half of the wall, but fingerlike extensions reached the epicardium. Multiple microscopic sections revealed no evidence of recent infarction. The QRS pattern in the precordial leads corresponded rather closely to the location of the infarct at autopsy, but the RS-T and T-wave abnormalities, which had led to a mistaken diagnosis of a recent infarct, were probably due to the pericarditis. Fixed RS-T abnormalities associated with an old infarct and independent of the pericarditis constituted a possible alternative.

CASE 29.—A previously healthy man, 66 years of age, was suddenly stricken with severe, oppressive retrosternal pain which radiated to both arms and led to hospitalization six and one-half hours later. No cardiac glycosides were given. Death occurred from bronchopneumonia on the twenty-eighth day.

Electrocardiographic Findings.—An electrocardiogram obtained nineteen hours after the onset of the present illness is reproduced in Fig. 3,*E.* A QS complex was present in Leads V_1, V_2, and V_3 and a broad Q, abnormally large in relation to the subsequent R, was found in V_4, V_5, and V_6. The abnormalities in the initial phase of the QRS were indicative of a large anterior infarct, extending into the septum and into the lateral wall of the left ventricle. The RS-T junction was moderately elevated in Lead V_2, but the segment displayed the normal upward concavity. However, in Leads V_3, V_4, V_5, and V_6 there was not only an abnormal RS-T elevation, but also an RS-T and T-wave contour typical of recent infarction. The inverted P and QR complex of Lead aV_L and the exceptionally tall late R wave in aV_R suggested that the potential variations of the posterobasal aspect of the left ventricle were transmitted to both upper extremities. Because of the simultaneous reference of positive potentials to both upper extremities, the late R of Lead I was relatively small in amplitude and the findings in this lead were consequently suggestive of infarction.

Pathologic Findings.—The heart weighed 380 grams and exhibited a recent organizing infarct, involving the entire apical two-thirds of the anterior wall, extending into the lateral aspect of the apex and also through the septum to the posterior part of the apex, as outlined in Fig. 6.

Fig. 6.—Roentgenogram of the injected heart of Case 29.

:t was transmural in its anterior portion and involved the subendocardial one-half in its lateral portion. The electrocardiographic findings in the first four precordial leads corresponded closely with the anterior and septal portions of the infarct, but those in V_5 and V_6 were more marked than would have been expected from the limitation of the lateral portion of the infarct to the apical segment. The absence of signs of the posteroapical infarction from Lead aV_F was probably due to horizontal position of the heart.

CASE 30.—A woman, 64 years of age, who had had hypertension for years, gave a typical history of myocardial infarction nine hours before hospitalization. Death occurred fifteen and one-half hours after admission.

Electrocardiographic Findings.—An electrocardiogram was obtained fourteen hours after the onset of the pain, but is not reproduced because of its similarity to that in Case 29 (Fig. 3,*E*). This electrocardiogram was diagnostic of a large, recent anterior infarct, extending into septum and lateral wall.

Pathologic Findings.—The heart weighed 437 grams and exhibited a recent transmural infarct, similar in position to that in Case 29 (Fig. 6), except that it extended into the apical one-half of the lateral wall. The electrocardiogram conformed closely with the lesion of the anterior, septal, and lateral walls, but failed to reveal the infarction of the posterior aspect of the apex because of the horizontal position of the heart.

CASE 31.—A man, 62 years of age, had been in good health until the day before hospital admission, when he had an attack of retrosternal pain, lasting ten minutes. The pain recurred on the afternoon of admission and lasted two hours. After a brief hiatus, it returned in the evening and necessitated hospitalization. Blood pressure was at shock levels during the eleven-day period in the hospital.

Electrocardiographic Findings.—An electrocardiogram obtained twenty-one hours after the second attack of pain and before the administration of cardiac glycosides is reproduced in Fig. 3,*F*. Lead V_1 showed an initial R of 2.0 mm. and Lead V_2, an initial R of 0.5 millimeter. A QS complex present in Leads V_3, V_4, and V_5 was indicative of the central zone, whereas a QR complex of low voltage in Leads V_6, aV_L, and aV_F was probably representative of a marginal zone of subendocardial infarction. Thus, the electrocardiogram gave evidence of a large anterior infarct, which extended into the lateral and posterior aspects of the apex, and the T-wave pattern indicated that it was of recent origin. The standard leads were of exceptionally low voltage and were strongly suggestive of infarction.

Pathologic Findings.—The heart weighed 480 grams and showed a large infarct, involving the apical two-thirds of the anterior aspect of the left ventricle and the apical one-third of the lateral and posterior aspects and the apical one-half of the interventricular septum. The infarct was transmural on the anterior surface and involved the subendocardial one-half in the lateral and posterior aspects. The location of the infarct was thus comparable to that in Case 29 (Fig. 6). In addition, there was an old, completely healed subendocardial infarct in the anteroseptal area at the base of the ventricle just proximal to the recent infarct. There was good correlation between the position of the recent infarct, as determined from the electrocardiogram and as demonstrated at autopsy, except for the fact that the electrocardiogram showed no definite signs of septal involvement.

CASE 32.—A man, 57 years of age, who had had hypertension for sixteen years, gave a history of an acute onset of painless dyspnea three weeks before admission to the hospital. Despite digitalization by his family physican, progressive failure developed. The patient was moribund on admission and died twenty-two hours later.

Electrocardiographic Findings.—An electrocardiogram resembled the last tracing in Case 21 (Fig. 1), and, consequently, is not reproduced. A diagnosis was made of a large, recent anterior infarction, extending into the lateral wall of the apex. The standard leads showed evidence of left ventricular hypertrophy, but were not diagnostic of infarction.

Pathologic Findings.—The heart weighed 704 grams and showed a recent infarct of the anterolateral wall of the left ventricle, resembling that in Case 21 (Fig. 2). This was partially superimposed upon an older anterior infarct, which extended into the septum in the four apical segments. The electrocardiogram revealed the anterolateral infarct, but failed to show definite evidence of the septal lesion.

CASE 33.—A man, 50 years of age, was admitted to the hospital in advanced congestive heart failure with a history of dyspnea and intermittent, stabbing retrosternal pain during the antecedent six months. There were physical signs of syphilitic aortic insufficiency. Death occurred forty-six hours after admission.

Electrocardiographic Findings.—An electrocardiogram obtained on the first hospital day, after 0.6 mg. of digitoxin, is reproduced in Fig. 3,*G*. Attention is directed to the 2.0 mm. initial R wave in Lead V_1, the QS deflection in V_2 and V_3, and the QR complex with abnormal Q in V_4, V_5, and V_6. From the findings in Leads V_4, V_5, and V_6, the presence of an organizing subendocardial infarct in the anterolateral wall of the apex was postulated, and from the findings in V_2 and V_3, the presence of an organizing transmural infarct higher in the anteroseptal wall was predicted. The limb leads showed signs compatible with an ischemic zone or with left ventricular hypertrophy, but not diagnostic of infarction.

Pathologic Findings.—The heart weighed 518 grams as the result of left ventricular hypertrophy secondary to syphilitic aortic insufficiency. There was an organizing infarct of the anterolateral wall of the three apical segments, closely comparable in size and position with that in Case 22 (Fig. 4). This infarct involved the subendocardial half of the lateral wall in the apical two segments, thus conforming with the electrocardiographic findings. However, the distribution in the anterior wall was the reverse of that predicted from the electrocardiogram in that the infarct was transmural in the apical two segments and subendocardial in the third segment. The QS complex in Leads V_2 and V_3 could not have been derived from the intact basal one-half of the anterior wall. The counterclockwise rotation revealed in the unipolar extremity leads may have displaced the transitional zone sufficiently to the right so that Leads V_2 and V_3 reflected the potential variations of the anteroseptal portion of the apex, which was the site of the transmural infarct, whereas Leads V_4, V_5, and V_6 reflected the potential variations of the anterolateral aspect of the apex, which was the site of a subendocardial infarct. It is also possible that the QS complex in V_2 and V_3 was a manifestation of the septal infarction. The normal initial R in V_1 is against this hypothesis, but might have been derived from activation of the free wall of the right ventricle.

CASE 34.—A previously healthy man, 47 years of age, was suddenly seized with constrictive retrosternal pain, radiating down both arms, followed by syncope and circulatory collapse. He died on the eleventh hospital day. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained on the first hospital day, approximately twenty-four hours after the onset of the pain, is reproduced in Fig. 7,*A*. The initial phase of the QRS was upright in all precordial leads. This R wave was 3.0 mm. in amplitude in Lead V_1 and 1.0 mm. in V_2, and then fell off to 0.5 mm. in V_3, V_4, and V_5, and then increased to 1.0 mm. in Lead V_6. The decrease in the amplitude of the R wave, as the electrode was moved from positions over the right ventricle to positions over the left ventricle, was abnormal and, coupled with the marked RS-T elevation and monophasic, upright T wave, led to the diagnosis of a recent, large anterolateral infarct. To explain the unusual finding of an initial upright rather than a downward deflection in leads over the infarct, it was postulated that the infarct either was patchy in distribution through the wall or failed to involve a thin subendocardial layer of muscle. Left bundle branch block was excluded by the absence of prolongation of the QRS interval. Two further electrocardiograms on the third and ninth hospital days showed essentially the same QRS pattern as in the original tracing, including an abnormally small but distinct initial R in the last five precordial leads. Lead aV_L displayed a QR complex with borderline Q of .02 second duration and 25 per cent of the succeeding R, followed by an elevated RS-T junction and inverted T wave. The QRS-T pattern in Lead aV_L was compatible with the findings obtained over a marginal zone of subendocardial infarction. However, if the QRS-T pattern in aV_L had been transmitted from the apical portion of the lateral wall to the left arm, the cardiac position should have led to the recording of an upright rather than an inverted P wave in Lead

aV_L.[13] The inverted P wave, prominent Q, tall late R, and sharply inverted T wave of Lead aV_L simulated the pattern which may be obtained in normal subjects through esophageal leads at or slightly above the level of the atrioventricular groove. The potential variations of this region may be transmitted both to the left and the right arms when the heart is rotated about a transverse axis in such a way as to carry the apex backward and tilt the base upward. Backward rotation on a transverse axis was borne out in this case by the tall, late R wave in Lead aV_R, which was derived from activation of the posterobasal wall of the left ventricle. Because of the position of the heart in this case, the findings in aV_L might have represented a normal variant and could not be regarded as diagnostic of infarction. The pattern most strongly suggestive of infarction was found in standard Lead I. The Q wave in Lead I was similar to that in aV_L, but the R wave in Lead I was greatly reduced over that in aV_L because positive potentials were being referred to both upper extremities during the latter part of cardiac activation and thus R_1 constituted the difference between the late R waves of Leads aV_L and aV_R. The elevated RS-T_1 represented the reciprocal of the RS-T depression in aV_R. Since the Q wave registered through the left arm component of Lead I may have been a normal variant, the findings in the standard leads could not be regarded as pathognomonic of infarction.

Pathologic Findings.—The heart weighed 617 grams and showed a large, recent infarct, which involved the entire anterolateral wall, the left half of the septum and the subendocardial half of the posterior wall in the apical two segments, the free portion of the anteroseptal wall and adjoining anterior half of the left side of the septum in the third, fourth, and fifth segments, and the anterior half of the left side of the septum in the sixth segment, as indicated by the areas of avascularity in the roentgenogram (Fig. 8). Microscopic sections showed that the infarct extended through the entire thickness of the anterior wall, including the papillary muscles and subendocardial layer, and failed to substantiate the ante-mortem explanation for the initial R waves in the precordial leads. In view of the electrical position of the heart, the possibility was considered that the apex had been carried far enough backward to impair transmission of its potential variations to precordial Positions 3, 4, and 5, and thus indirectly favor transmission of the potential variations of more basal portions of the anterolateral wall to these regions. However, the fact that the anterior portion of the infarct involved almost the entire wall left little muscle at the base to serve as a source for the R wave and necessitated search for another explanation. Consideration was given to the possibility that the Purkinje network in the anterior half of the left side of the septum was destroyed by the infarct in this area. Under these circumstances, any residual intact muscle in the anterior half of the septum must have been activated by way of the Purkinje plexus of the right ventricle. Positive potentials resulting therefrom would have been transmitted toward the left side of the precordium and might have accounted for the initial R in Leads V_3, V_4, and V_5. Since the negative potentials would have been directed toward the right ventricular cavity, a small Q would have been expected preceding the RS complex of V_1. However, this Q might be eliminated if the impulse reached and started to activate the free wall of the right ventricle simultaneously with its penetration of the septum. Another feature which had to be rationalized with the foregoing hypothesis was the initial Q in left ventricular lead aV_L. Since the posterior half of the basilar two-thirds of the septum was intact at autopsy, the vector associated with its activation may have taken the usual direction, and, consequently, negative potentials may have been transmitted backward to the posterobasal wall of the left ventricle. Since the electrical position of the heart favored reference of the potential variations of the posterobasal aspect of the left ventricle to the left arm, the Q in aV_L may have originated in this manner and may have represented a normal variant, unrelated to the infarct of the lateral aspect of the apex found at autopsy. If so, the QR complex of Lead I was also independent of the infarction. Although a dogmatic assertion as to the source of the Q waves in Leads aV_L and I was impossible in this case, our contention that they might have represented a normal variant is supported by the findings in another patient, to be reported in detail later. Tracings in the recumbent position revealed abnormal QR complexes in Leads aV_L and I, resembling those in the present case, whereas tracings in the erect position showed a notch at the base of the upstroke of the R in place of the Q wave. This patient subsequently came to autopsy and no evidence of myocardial infarction was found.

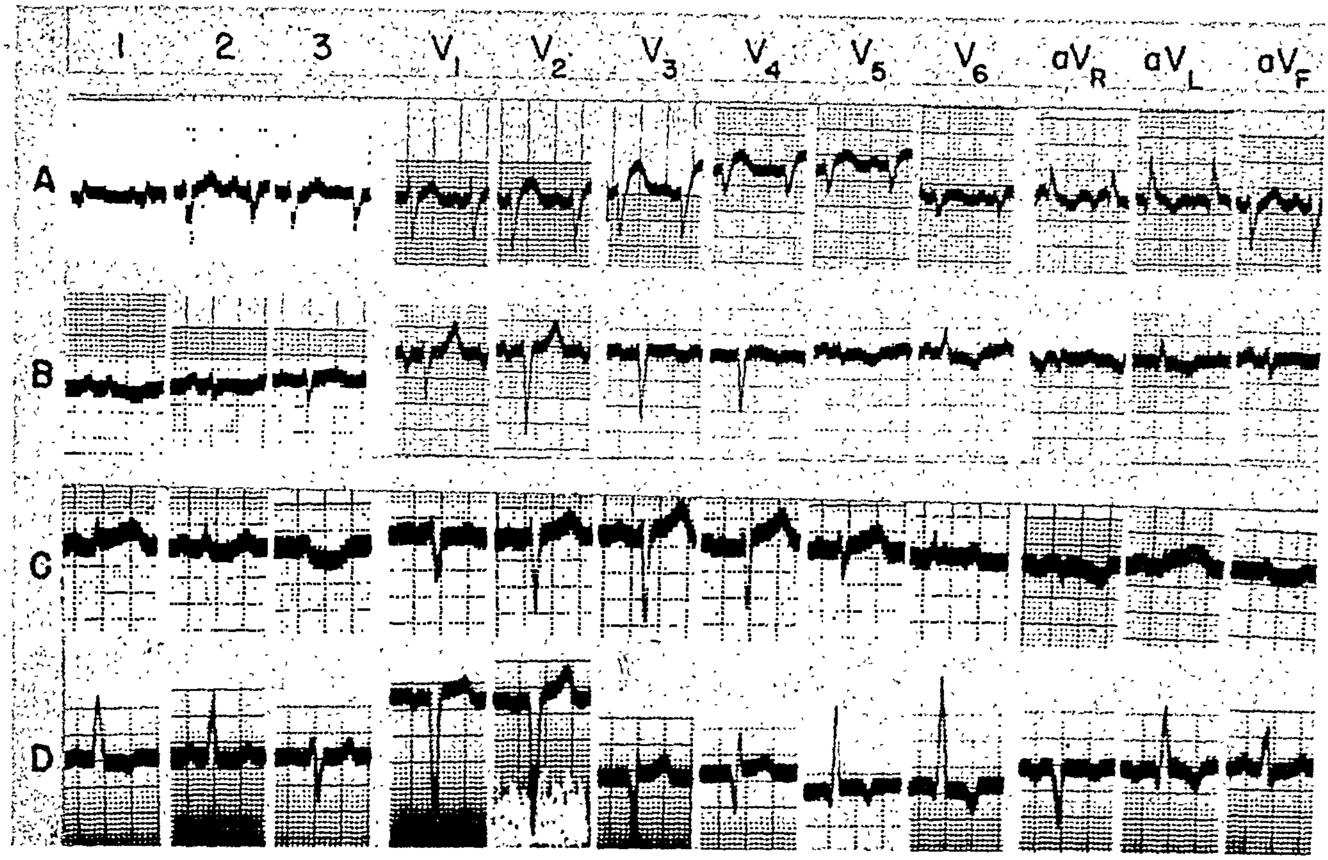

Fig. 7.—Recent anterolateral infarction with atypical QRS-T pattern. *A*, Case 34; *B*, Case 35; *C*, Case 36; *D*, Case 37.

Fig. 8.—Roentgenogram of the injected heart of Case 34, showing recent anterolateral infarct demarcated by its avascularity.

CASE 35.—A man, 58 years of age, was suddenly stricken with prolonged retrosternal pain one month previously and had recurrent attacks of transient constriction during the interim, despite strict confinement to bed in his home. Following a second prolonged attack, he was admitted in shock and remained in circulatory collapse until death on the eighth hospital day. No cardiac glycosides were given.

Electrocardiographic Findings.—Electrocardiograms were obtained on the third and seventh hospital days, and the latter is reproduced in Fig. 7,*B*. The contour of the P waves in Leads V_1 and V_2 suggested that the electrode was in the vicinity of the right atrium. The QRS complexes were comparable to those in Case 34 in that the initial phase was upright in all precordial leads, but decreased from an amplitude of 1.0 to 2.0 mm. in Leads V_1 and V_2, to 0.5 mm. in V_3, V_4, and V_5, and then increased in V_6. The initial deflection was downward in Lead aV_L, but the QR complex in this lead was classed as borderline, since the Q was only 0.02 second in duration, 1.0 mm. in depth, and 25 per cent of the succeeding R. The dome-shaped RS-T segment and inverted T wave in Lead V_4 were strongly suggestive of the pattern associated with organizing infarct. The T wave was inverted in Leads V_5, V_6, and aV_L, but the slight depression of the RS-T junction in these leads was atypical. The standard leads were abnormal, but were not diagnostic of infarction. A diagnosis of a large anterolateral infarct was made and because of the preservation of the R wave, it was postulated that the infarct either was patchy in distribution or had spared a thin layer of subendocardial muscle.

Pathologic Findings.—The heart weighed 494 grams and exhibited evidence of an organizing infarct of approximately one month's duration, involving the anterior, lateral, and septal walls of the apical half of the left ventricle in a fashion similar to that in Case 34 (Fig. 8). This lesion extended subendocardially into the apical one-third of the posterior wall. In addition there was an infarct of approximately one week's duration, involving the posterobasal half of the left and right ventricles and the adjacent interventricular septum. Although the anterolateral infarct appeared to be transmural on gross examination, multiple microscopic sections in this case showed a few islands of intact muscle. These patches may have accounted for the minute initial R in the precordial leads over the left ventricle, particularly in view of the fact that the opposing negative potentials ordinarily derived from the posterior wall were reduced in this case by the extensive posterobasal infarction. The latter had been missed in the electrocardiographic interpretation, since Lead aV_F of both electrocardiograms displayed an RS complex and low, upright T wave. The findings in aV_F had been attributed to transmission of the potential variations of the right ventricle to the left leg, as the result of horizontal position. Since the basal portion of the right ventricle was infarcted, it is possible that the RS complex was derived from the intact apical portion of the right ventricle.

CASE 36.—A man, 65 years of age, gave a history of dyspnea and occasional brief attacks of retrosternal oppression on exertion during the antecedent two years, but had had no protracted retrosternal pain until the day of admission. He was brought to the hospital in shock seven hours after the onset of an exceptionally severe attack of retrosternal oppression. Blood pressure was unobtainable and profound circulatory collapse persisted, ending in death fifty-nine hours later.

Electrocardiographic Findings.—An electrocardiogram obtained eight hours after the onset of the pain is reproduced in Fig. 7,*C*. The initial phase of the QRS was upright in all precordial leads and measured 2.0 mm. in Lead V_1, 3.0 mm. in V_2, and dropped to 2.0 mm. in Leads V_3, V_4, and V_5, and increased to 5.0 mm. in V_6. The T wave was upright in all precordial leads and the RS-T segment displayed the normal upward concavity. The RS-T take-off was above the isoelectric line in all precordial leads, but was considered definitely abnormal only in V_4, where it was elevated 3.5 millimeters. The reduction in the amplitude of the R wave in Leads V_3, V_4, and V_5 and the abnormally elevated RS-T junction in V_4 were suggestive of a recent subepicardial or patchy transmural infarct, involving the anterior and anterolateral aspects of the left apex. The findings in Leads aV_L, aV_F, and I, II, and III were much more striking than those in the precordial leads. Lead aV_L displayed an upright P wave, a QR complex of very low voltage, a high RS-T take-off, a straightened RS-T segment, and a monophasic, upright T wave typical of the stage of injury of recent lateral infarction. Lead I showed similar changes in the RS-T segment.

and T wave, but was less typical of infarction than aV_L because it lacked a Q wave. Lead aV_F displayed reciprocal RS-T depression, which was carried over into Lead III. Because of the findings in Leads aV_L and I, a diagnosis was made of recent infarction of the lateral wall of the left ventricle. Unfortunately, a second electrocardiogram was not obtained.

Pathologic Findings.—The heart weighed 534 grams and showed evidence of a recent, large infarct of the anterior wall of the left ventricle, the lateral aspect of the apex, and the interventricular septum, comparable in size and position to that in Case 34 (Fig. 8). Microscopic sections through the septum, anterior wall, and lateral aspect of the apex showed that the infarct was transmural. Thus, there was a considerable discrepancy between the surface area and thickness of the infarct, as predicted from the precordial electrocardiogram and the actual findings at autopsy. Two explanations for this discrepancy were given serious consideration. It is possible that the infarct was originally confined to the anterolateral aspect of the apex and extended during the fifty-eight hour period after the electrocardiogram was made. However, the profound degree of shock on admission suggested the presence of a large infarct, comparable in size to that found at autopsy. Since the electrocardiogram was obtained only eight hours after the onset of the pain, it seemed more likely that the myocardial degeneration had not progressed to the point of complete obliteration of the response to the activating impulse.

CASE 37.—A man, 47 years of age, had had chills and fever for two months and repeated attacks of retrosternal oppression for one week prior to hospital admission. Physical examination revealed evidence of mitral and aortic stenosis and insufficiency. Numerous petechiae and a positive blood culture for *Streptococcus viridans* established the diagnosis of subacute bacterial endocarditis. In spite of penicillin therapy, the patient expired on the seventh hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained on the first hospital day, before the administration of cardiac glycosides, is reproduced in Fig. 7,*D*. Attention is directed to the QS complex in Leads V_1 and V_2 and the QR deflection with abnormally large Q in V_3 and V_4 and with small but slurred and prolonged Q in V_5 and aV_L. On the basis of these findings, a diagnosis was made of a relatively large infarct of the septum and anterior wall, extending subendocardially into the lateral wall of the apex. The RS-T segments and T waves were atypical, but compatible with a recent infarct. The pattern in Lead V_6 and that in the standard leads was in keeping with left ventricular hypertrophy, but was not diagnostic of infarction.

Pathologic Findings.—The heart weighed 743 grams and showed evidence of chronic rheumatic mitral and aortic valvulitis complicated by subacute bacterial endocarditis. An organizing subendocardial infarct was found in the apical five-sixths of the anterior wall, the apical one-half of the lateral wall, the apical one-third of the posteroseptal wall of the left ventricle, and the apical two-thirds of the left side of the septum. The position of the infarct was similar to that in Case 23 (Fig. 5), except for limitation to the subendocardial half of the outer wall of the left ventricle and left half of the septum. No point was found where the infarct extended completely through the wall. The QS deflections in Leads V_1 and V_2 were apparently due to the septal lesion, and the QR complexes in V_3 and V_4 corresponded closely with the subendocardial infarct of the anteroseptal wall, whereas those in Leads V_5, V_6, and aV_L could be correlated with the less extensive involvement of the lateral wall. The extension into the subendocardial one-third of the posteroseptal wall was not evident in aV_F, despite the fact that this lead reflected the potential variations of the left ventricle.

CASE 38.—A man, 57 years of age, was admitted to the hospital on March 12, 1947, for treatment of diabetes mellitus complicated by the Kimmelstiel-Wilson syndrome. He had had typical intermittent claudication, but denied other cardiovascular symptoms. On April 4 diarrhea developed and approximately ten stools daily were passed during the next five days. On April 8 he was suddenly seized with severe dyspnea unaccompanied by chest pain. Examination revealed a regular cardiac rate of 240, which was abruptly halved by carotid sinus pressure. Sinus rhythm soon returned spontaneously, but marked pulmonary edema persisted, leading to digitalization on April 10. Partial alleviation was obtained until 1:00 A. M. on April 15, when extreme orthopnea recurred and persisted until death fifteen hours later.

Electrocardiographic Findings.—Electrocardiograms are reproduced in Fig. 9. A routine tracing taken on March 31 showed a 2.0 mm. Q wave in Lead aV_F, which was approximately 15 per cent of the R wave in the same lead. Although this Q wave, when considered as an isolated finding, was not abnormal, the fact that it was followed by a slurred upstroke of 0.04 second duration suggested that the QR complex was abnormal. The pattern in Leads aV_F, II, and III

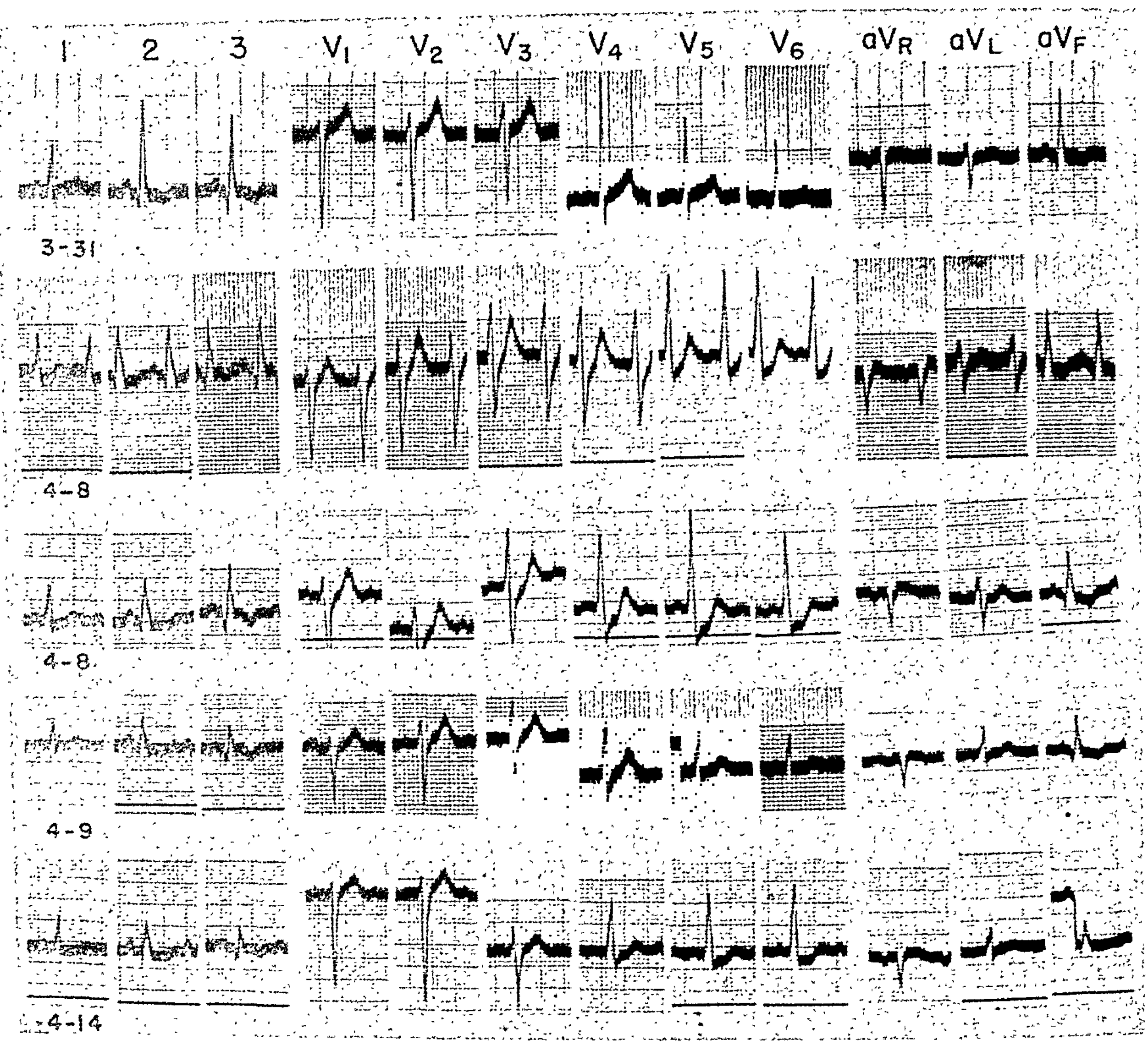

Fig. 9.—Serial electrocardiograms of Case 38, showing old posterior infarction in tracing made March 31, and subsequent ischemia of the subendocardial portion of the anterolateral wall.

of March 31 was compatible with, but not pathognomonic of a patchy subendocardial infarct of the posterior wall of the left ventricle. The QRS of the precordial leads of March 31 was entirely normal and the slight elevation of the RS-T junction in Leads V_1 through V_5 was considered normal in view of the relatively high voltage of the upright T wave in these leads and the upward concavity of the RS-T segment. In the first tracing, April 8, which was obtained two and one-half hours after the onset of the dyspnea, there was a regular ventricular rate of 120 per minute. The P waves appeared to correspond with those of the previous tracing, but close inspection of Leads aV_F, II, and III revealed an additional P wave in each cycle, coming immediately after the R and giving an auricular rate of 240. Therefore, a diagnosis of auricular tachycardia with 2:1

block was made. The most striking electrocardiographic change consisted in a marked depression of the RS-T junction, which amounted to 5.0 mm. in Lead V_6, 3.0 mm. in V_5 and V_4, and 2.0 mm. in Leads V_3 and aV_F. On the other hand, there was no significant change in the QRS complex or T wave, apart from a displacement of the transitional zone to the left. Another tracing taken three hours later on April 8 showed return of sinus rhythm, but persistence of the marked RS-T depression. The suddenly developing RS-T depression was attributed to acute ischemia of the subendocardial layer of muscle, most marked in the anterolateral aspect, but extending into the anteroseptal and posterior walls of the left ventricle. From the absence of significant QRS change, it was inferred that either the ischemia was patchy in distribution or it had not progressed to the point of interfering with the myocardial response to the activating impulse. The diagnosis of transient subendocardial ischemia was confirmed by the disappearance of the RS-T depression on April 9 and the return to a pattern closely resembling that of the control tracing of March 31. In the meantime the heart had shifted from a vertical to an intermediate position with concomitant reduction in the amplitude of the R wave in Lead aV_F and consequent increase in the QR ratio to 33 per cent. The appearance of a disproportionately large Q wave in Lead aV_F in conjunction with a slurred, abnormally prolonged ascending limb of the R wave led to a definite diagnosis of posterior infarction. RS-T depression reappeared in Leads V_4, V_5, and V_6 of the tracing of April 14, but its significance was debatable because of the administration of digitalis.

Pathologic Findings.—The heart weighed 450 grams and showed very marked coronary sclerosis. There was an old, completely healed infarct, extending in patchy fashion through the subendocardial two-thirds to three-fourths of the posterior wall, as represented by the broken line in Fig. 10. This infarct was apparently responsible for the pattern in Lead aV_F of the control tracing of March 31. There was a very recent, ringlike infarct, involving the subendocardial one-half of the entire circumference of the left ventricle. By microscopic examination, this infarct was judged to be less than twenty-four hours in duration. If the age of the infarct was correctly interpreted, the transient RS-T depression on April 8 was attributable to acute ischemia of the subendocardial muscle, which later became infarcted. The last tracing on April 14 was obtained thirty hours before death, and it is problematic as to whether the acute subendocardial infarct demonstrated at autopsy was present at that time. However, both the history and microscopic findings suggested that the terminal subendocardial infarction occurred after the last electrocardiogram.

CASE 39.—A man, 80 years of age, gave a history of dyspnea and transient retrosternal distress on exertion for the preceding six months and was admitted to the hospital in shock, complicating a prolonged bout of severe retrosternal pain. He remained in circulatory collapse and died on the seventh hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained about six hours after the onset of the second attack of prolonged retrosternal pain is reproduced in Fig. 11,*A*. A QS complex was found in Leads V_1 through V_5, and a minute, slurred R wave was recorded in V_6. A QS deflection as far to the left as precordial Positions 4 and 5 pointed toward an infarct of the anterior and anterolateral wall of the left ventricle. The diagnosis would have been more certain if an initial R had been present in Leads V_1 and V_2. The electrode in these positions was in the vicinity of the right atrium, as judged by the contour of the P wave. The QS complex recorded in Leads V_1 and V_2 was compatible with extension of the infarct into the septum. There was an abnormal RS-T elevation of 3.0 mm. in Lead V_2 and a borderline displacement of 2.0 mm. in V_1, V_3, and V_4. The T wave was upright in Leads V_1 through V_5 and flattened in V_6. The RS-T segment showed a normal upward concavity and was thus atypical for recent myocardial infarction. It is noteworthy that both the QS and the RS-T and T-wave complexes in the first four precordial leads corresponded closely in contour with the reciprocal of the pattern in Lead aV_F. Two subsequent tracings during the next five days showed no significant change in the contour of the RS-T segment and T wave. From the unipolar limb leads, the heart appeared to be in vertical position. The standard leads were abnormal, but were not diagnostic of recent myocardial infarction.

Pathologic Findings.—The heart weighed 429 grams and exhibited a large, transmural anterior infarct approximately one week in duration, which extended into the lateral wall of the apex and into the apical three-fourths of the interventricular septum in a manner almost identical with that in Case 34 (Fig. 8). The transmural infarction of the anterolateral portion of the apex was apparently responsible for the QS complex in Lead V_5 and the transmural infarct of the apical three-fourths of the anteroseptal wall and adjoining interventricular septum accounted for the QS complex in the first four precordial leads. The preservation of the normal upward concavity of the RS-T segment was an uncommon finding in recent anterior infarction and the absence of serial changes in the RS-T and T-wave complex over a period of six days was most extra-

Fig. 10.—Roentgenogram of the injected heart of Case 38, showing old posterior infarction outlined in dotted lines and recent subendocardial infarction outlined in solid lines.

ordinary. These unusual features were probably referable to the complete infarction of the anterior wall found on microscopic examination. A completely destroyed anterior wall should produce no electromotive force and should merely serve as a conducting window for the precordial transmission of potentials referred to the cavity during both activation and repolarization of the intact posterior wall.[4,14] Activation of the hypertrophied but uninfarcted posterior diaphragmatic wall resulted in the transmission of positive potentials to the left leg, recorded as a tall R in aV_F, and in the simultaneous transmission of opposite negative potentials to the cavity. The registration of a QS complex in Leads V_1 through V_4, which was almost an exact reciprocal of the R in aV_F, suggested that the QS deflection represented cavity potentials, unmodified in their transmission through a transmurally infarcted septum and anterior wall. Repolarization

of the hypertrophied posterior diaphragmatic wall was manifested by a depressed, upwardly convex RS-T segment and inverted T wave in aV_F and should have produced an opposite pattern in a cavity lead. The repeated registration in the first four precordial leads of an elevated, upwardly concave RS-T segment and upright T wave, which constituted almost an exact reciprocal of the pattern in aV_F, suggested that the RS-T and T-wave complex in these leads represented cavity potentials derived from repolarization of the posterior wall and unmodified in their transmission through a dead anterior wall. In comparison of the electrocardiogram in Case 24 with that in the present case, a striking similarity will be noted in the QS deflections of the first five precordial leads, but a significant difference will be found in the RS-T segments. The abnormally elevated RS-T junctions and convex RS-T segments in Leads V_1 through V_4 in Case 24 simulated those produced by injury localized to the subepicardial layer and indicated the presence of muscle in this layer that was injured, but not dead.

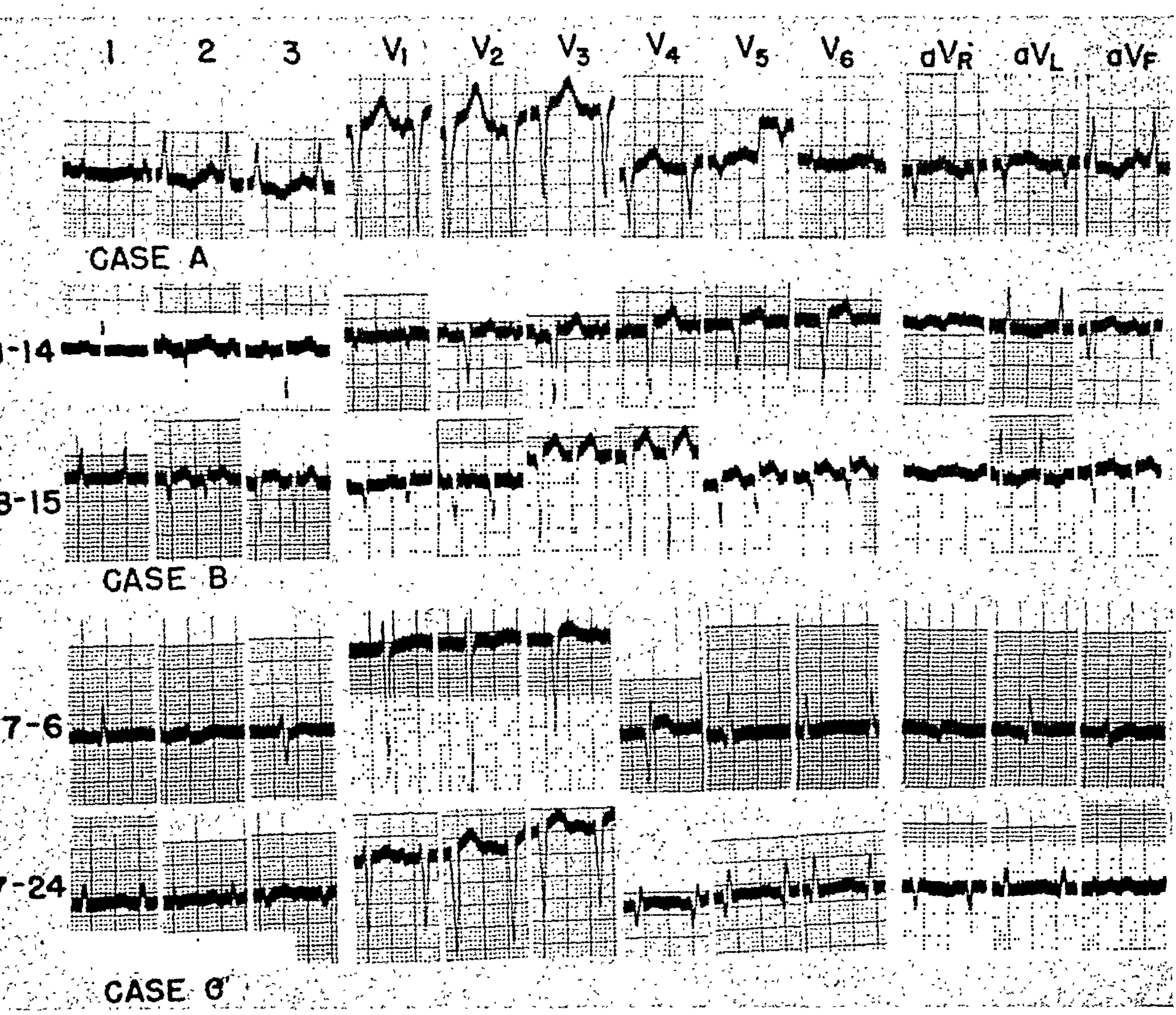

Fig. 11.—Recent anterolateral infarction. *A*, Case 39; *B*, Case 41; *C*, Case 42.

CASE 40.—A man, 58 years of age, was in good health until one month before hospital admission, when typical symptoms of diabetes mellitus developed. Two weeks before entry he was suddenly seized with sharp precordial pain and dyspnea, lasting four hours, and four days prior to entry he had a second similar attack. The patient was mentally confused throughout his entire hospital stay and died suddenly on the seventeenth day.

Electrocardiographic Findings.—Electrocardiograms were obtained on the third, fifth, and seventh hospital days, but are not reproduced because of their close resemblance to those in Case 39 (Fig. 11,*A*). Leads V_1 through V_4 displayed a QS complex, a 2.0 mm. elevation of the RS-T junction, an upwardly concave RS-T segment, and upright T wave similar to the corresponding leads in Case 39. In Lead V_5 there was a notched QS complex, an isoelectric RS-T, and low upright T wave. The QRS pattern in Leads V_6, aV_L, and aV_F was almost identical with that in Case 39. Lead I displayed a small QS complex, rather than an R wave, because of the fact that the negative potentials referred to the left arm were of greater magnitude than those referred to the right arm. Furthermore, no significant change in the QRS-T complex of any precordial or limb lead was demonstrable in the electrocardiograms taken on the fifth and seventh hospital days. Unfortunately, no further tracings were obtained during the last ten days in the hospital. The QS complex in Leads V_1 through V_5 pointed strongly toward a large infarct of the anterior and anterolateral walls and the preservation of the normal upward concavity of the RS-T segment and the lack of serial changes in the RS-T and T-wave complex over a five-day period suggested either that the infarct was old and healed or that it was recent and had destroyed the entire anterior wall, as in the previous case.

Pathologic Findings.—The heart weighed 516 grams and exhibited an organizing anterior infarct almost identical in size and position with that in Case 39. On microscopic examination the infarct was judged to be about three weeks of age and was found to involve the entire thickness of the anterior wall and septum. Thus, the complete transmural infarction of the anteroseptal portion of the left ventricle and interventricular septum could account for the QS complex, the upwardly concave RS-T segment, and absence of serial change in the RST-T complex of Leads V_1 through V_4.

CASE 41.—A woman, 74 years of age was well until a fortnight before admission to the hospital, when she had an attack of severe epigastric and retrosternal oppression which lasted twenty-four hours. The patient was admitted in severe congestive heart failure and died three days later.

Electrocardiographic Findings.—Electrocardiograms obtained on August 14, five hours after admission and before administration of cardiac glycosides, and on the following day, after administration of 0.4 Gm. of digitalis, are reproduced in Fig. 11,*B*. The QS complex found in all precordial leads on August 14 was strongly suggestive of a very large anterior and anterolateral infarct, but additional leads to the right of V_1 and to the left of V_6 would have been desirable to delineate the lesion. The elevated RS-T junction, upwardly concave RS-T segment, and erect T waves in Leads V_2 through V_6 were compatible with complete transmural infarction, as brought out in the discussion of Case 39. The pattern in the precordial leads was an approximate reciprocal of the prominent R, depressed, upwardly convex RS-T, and inverted T of aV_L. It was believed that the pattern in aV_L was derived from an uninfarcted basal portion of the lateral wall. The minute R and prominent S of aV_F were apparently transmitted from the posterior inferior surface of the right ventricle, as a result of horizontal position of the heart. The standard leads showed marked left axis deviation of a type compatible with left ventricular hypertrophy, but were not diagnostic of infarction. The tracing taken the following day showed auricular fibrillation with a ventricular rate of approximately 165. No significant change had occurred in the QRS complex or T wave. Slight upward concavity was still detectable in the RS-T segments of Leads V_3 and V_4, but those of V_5 and V_6 appeared straightened, perhaps because of a combination of digitalis and rapid heart rate. A third tracing taken on August 16, but not reproduced, showed resumption of sinus rhythm and return to a QRS-T pattern similar to that of the first tracing.

Pathologic Findings.—The heart weighed 422 grams and exhibited an organizing infarct corresponding to the area of avascularity in the roentgenogram (Fig. 12). The entire circumference of the left ventricle in the apical segment and the anteroseptal wall and septum in the second and third segments showed complete infarction of their entire thickness. In the second segment, the infarct extended into the subendocardial one-fourth of the lateral and posterior walls, and in the fourth segment it involved the subendocardial half of the anteroseptal wall. The remainder of the heart was intact and the infarct demonstrated at autopsy was, therefore, not as

large as that predicted from the electrocardiogram. The QS deflection and the upwardly concave RS-T segment and erect T in the first four or five precordial leads were apparently a manifestation of the complete transmural infarction of the apical three-fifths of the septum and anterior wall, and the pattern in V_6 may have been derived from this or perhaps from the circumscribed infarct in the lateral aspect of the apical segment. This case exemplifies the tendency to overestimate the size of the infarct from electrocardiographic interpretation when the heart and thorax are relatively small. An infarct of given size tends to produce Q-wave abnormalities in a greater number of precordial leads when the heart and thoracic cage are small than when large.

Fig. 12.—Roentgenogram of the injected heart of Case 41, showing anterolateral infarct demarcated by its avascularity.

CASE 42.—A man, 48 years of age, had had hypertension for twelve years, increasing exertional dyspnea for one year, and paroxysmal nocturnal dyspnea for three months, but denied chest pain. He was admitted to the hospital in marked congestive heart failure, remained decompensated in spite of intensive therapy, and died in circulatory collapse on July 26.

Electrocardiographic Findings.—Electrocardiograms obtained on July 6 and 24 are reproduced in Fig. 11,*C*. The first tracing, taken after the administration of a total of 6.0 mg. of Cedilanid parenterally during the preceding four days, showed auricular fibrillation with ventricular rate averaging 90 to 100 per minute. From the presence of a QS deflection in Lead V_3, a QR complex with an abnormally deep Q in V_4 and with an abnormally broad Q in V_5 and aV_L, in conjunction with a normal initial R in V_1 and V_2, a diagnosis was made of anteroseptal infarction, extending into the subendocardial portion of the aterolateral wall of the apex. Leads V_3 and V_4 displayed an abnormally elevated RS-T junction and upwardly convex RS-T segment and monophasic, upright T wave, which at first glance was suggestive of recent infarction; however, the marked shortening of the QT interval suggested that the RS-T and T-wave changes were due to the ex-

cessive doses of Cedilanid. This was supported by the resemblance of the RS-T and T-wave pattern in V_3 and V_4 to that produced by the administration of toxic doses of digitalis to cats.[15] On the other hand, the lack of evidence of marked digitalis effects in other leads left the interpretation in doubt. Cedilanid was discontinued on July 6 and daily doses of 1 cat unit of Digalen were given thereafter. In the tracing of July 24 the Q waves in Leads V_5 and V_6 had increased significantly in relation to the succeeding R. This suggested extension of the infarct farther into the subendocardial portion of the lateral aspect of the apex during the interim. The T waves in these leads were still flattened and were not characteristic of infarction. However, the former dome-shaped RS-T segment in Lead V_3 was replaced by an upwardly concave RS-T segment, and the Q-T interval had lengthened despite the increase in heart rate to 125 with restoration of sinus rhythm. This change was in keeping with decrease in digitalis effect and thus indirectly supported the premise that the former changes were due, at least in part, to the toxic effects of digitalis.

Pathologic Findings.—The heart weighed 523 grams and showed a large anterior infarct similar in location to that in Case 29 (Fig. 6), except for involvement of the subendocardial half of the entire lateral wall in the second segment as well as in the apical segment. The infarct of the apical two-thirds of the anteroseptal aspect of the left ventricle was confined largely to the subendocardial one-half of the wall and was judged to be at least two months of age, but showed areas of recent activity, which were probably secondary to the terminal shock. It would thus appear that the anteroseptal infarct had occurred at least one month prior to the tracing of July 6, and it is therefore probable that the RS-T and T-wave pattern in Leads V_3 and V_4 of this tracing was due largely to the excessive doses of Cedilanid. The infarct which involved the subendocardial one-half of the lateral aspect of the left ventricle in the apical two segments was judged to be approximately one week in duration and thus represented an extension during hospitalization, as was suggested by the increased depth of the Q waves in Leads V_5 and V_6.

CASE 43.—A man, 45 years of age, gave a history of an attack of prolonged retrosternal pain six months previously, from which he made a complete recovery. He had a second similar attack one month before hospitalization, followed by repeated paroxysms of nocturnal dyspnea. He was admitted to the hospital in acute pulmonary edema and became compensated during a four-day course of Cedilanid. He had no further episodes of thoracic pain and died from recurrent congestive failure five months later.

Electrocardiographic Findings.—An electrocardiogram obtained on the twenty-second hospital day, eighteen days after the discontinuance of Cedilanid, is reproduced in Fig. 13,*A*. The QRS interval measured 0.12 second in Leads V_5 and V_6 and only 0.08 to 0.09 second in the standard limb leads. Since the time elapsing from onset of the QRS to the beginning of the intrinsicoid deflection was 0.02 second in Lead V_1 over the right ventricle and 0.08 to 0.09 second in Leads V_5 and V_6 over the left ventricle, the conduction defect was located in the left ventricle. The registration of a Q wave in left ventricular leads is most unusual in left bundle branch block, but may occur when there is extensive infarction of the septum. Under these circumstances, a longer QRS interval would have been expected. On the other hand, the QR patterns of Leads V_5 and V_6 were typical of a conduction defect in the anterolateral wall of the left ventricle. The slurred Q wave of Lead V_6, which measured 0.04 second from onset to nadir, and the succeeding notched upstroke, which covered 0.05 second from onset to peak, pointed to a lesion, chiefly in the subendocardial layer, which caused retardation in the spread of the impulse through the wall. The descending limb of the Q wave of Leads V_6 and aV_L exhibited a notch similar to that occurring on the ascending limb of the R of V_6. This caused a lengthening of the time elapsing from onset to nadir of Q wave in Leads V_5 and aV_L to the unusually long interval of 0.06 second. The notched downstroke and subsequent precipitous upstroke in Lead V_5 and the steeper downstroke, but more gradual notched upstroke of V_6 were merely different manifestations of the same defect and were both attributable to a lesion of the subendocardial portion of the outer wall of the left ventricle. The QS pattern in Lead V_4 was attributed to transmural infarction of the apical portion of the anteroseptal wall, particularly in view of the 1.5 to 2 mm. initial R wave of V_1 and V_2, and the decrease to 0.5 mm. in Lead V_3. Since serial tracings taken over a period of five months showed no significant change in QRS or RS-T pattern, a diagnosis was made of an old infarct, involving the apical portion of the anterior and lateral walls of the left ventricle.

Pathologic Findings.—Autopsy disclosed an old, healed infarct, involving the apical half of the anterior and lateral wall of the left ventricle, comparable in distribution to that in Case 44 (Fig. 14), except that it extended for a short distance into the left side of the apical one-third of the septum. The lesion was characterized by dense fibrosis of the subendocardial one-half to two-thirds of the anterolateral wall with fingerlike projections to the epicardial surface. Thus, there was good correlation between the position of the anterolateral portion of the infarct as predicted from the electrocardiogram and as demonstrated at autopsy. The extension into the septum was not detected electrocardiographically.

CASE 44.—A man, 71 years of age, was struck by an automobile and was brought to the hospital in stupor with multiple rib fractures. Past history was not obtainable. Bronchopneumonia developed on the fourth day and caused death on the eighth day.

Electrocardiographic Findings.—An electrocardiogram obtained on the fifth hospital day, before the administration of cardiac glycosides, is reproduced in Fig. 13,*B*. The P-R interval was at the lower limit of normal. The initial phase of the QRS in the first four precordial leads consisted of an R wave, which measured 2.0 mm. in Lead V_1 and 4.0 mm. in V_2, and fell off to 2.0 mm. V_3, and to 0.5 mm. in Lead V_4. Leads V_5 and V_6 displayed a slurred Q wave 0.02 to 0.03 second in duration and approximately 50 per cent of the amplitude of the succeeding R. This was taken as evidence of an infarct involving the subendocardial portion of the anterolateral wall of the left ventricle. The dome-shaped RS-T segments and very slightly inverted T waves in these leads were suggestive of organization, but might have represented a fixed residue. More striking changes in the T wave were found in the first three precordial leads and consisted of sharp inversion associated with an elevated RS-T junction in V_1 and an approximately isoelectric take-off in the other leads. The question arose as to whether these changes were due to acute right ventricular dilatation or a recent anteroseptal infarction. The sharp downstroke in the P waves of Leads V_1 and V_2 suggested that the electrode was in the vicinity of the right atrium. The registration of a normal initial R in Leads V_1 and V_2 (which were considerably to the right of the septum) and the deeper inversion of the T waves in these leads than in Leads V_3 and V_4 (which were nearer to the septum) were strongly against recent anteroseptal infarction, but were in favor of acute right ventricular dilatation. The prominent late R wave in aV_R was probably transmitted from the posterobasal aspect of the left ventricle and suggested backward displacement of the apex. The prominent Q wave of aV_L was almost cancelled out in Lead I because of simultaneous initial negativity of the right arm. Consequently, the standard leads were not diagnostic of infarction.

Pathologic Findings.—The heart weighed 512 grams and exhibited an aneurysm of the anterolateral aspect of the left apex due to an old, completely healed infarct of the subendocardial three-fourths of the wall, as outlined in Fig. 14. There was satisfactory correlation between the infarct of the anterolateral wall of the apex and the abnormal QR pattern in Leads V_5, V_6, and aV_L. The abnormal RS pattern in V_3 and V_4 did not accurately portray the continuation of the infarct subendocardially into the anteroseptal wall, which should have produced a QS and QR deflection in these leads. The abnormally small R may have been derived from undetected islands of preserved muscle in the dense subendocardial infarct. A more likely alternative explanation was suggested by the backward rotation of the apex, deduced from the pattern in Lead aV_R. This may have carried the apex far enough away from the precordium to have hindred transmission of its potential variations to precordial Position 4 and thus may have indirectly favored reference of positive potentials from points to the right of or above the apical infarct. A patchy fibrosis was found in the subendocardial portion of the posterior wall, as represented by the stippling, but was not detected electrocardiographically. Autopsy also disclosed a moderate acute right ventricular dilatation, secondary to the bronchopneumonia. Although this seemed a better explanation for the inverted T waves in Leads V_1, V_2, and V_3 than the old, healed anteroseptal infarct, it was not altogether satisfactory, since greater right ventricular dilatation has been observed in association with erect T waves in these leads.

CASE 45.—A man, 56 years of age, gave a six-year history of angina pectoris. He had had two previous bouts of prolonged retrosternal pain, complicated by congestive failure, and was admitted to the hospital following a third similar attack. Death occurred on the thirtieth hospital day.

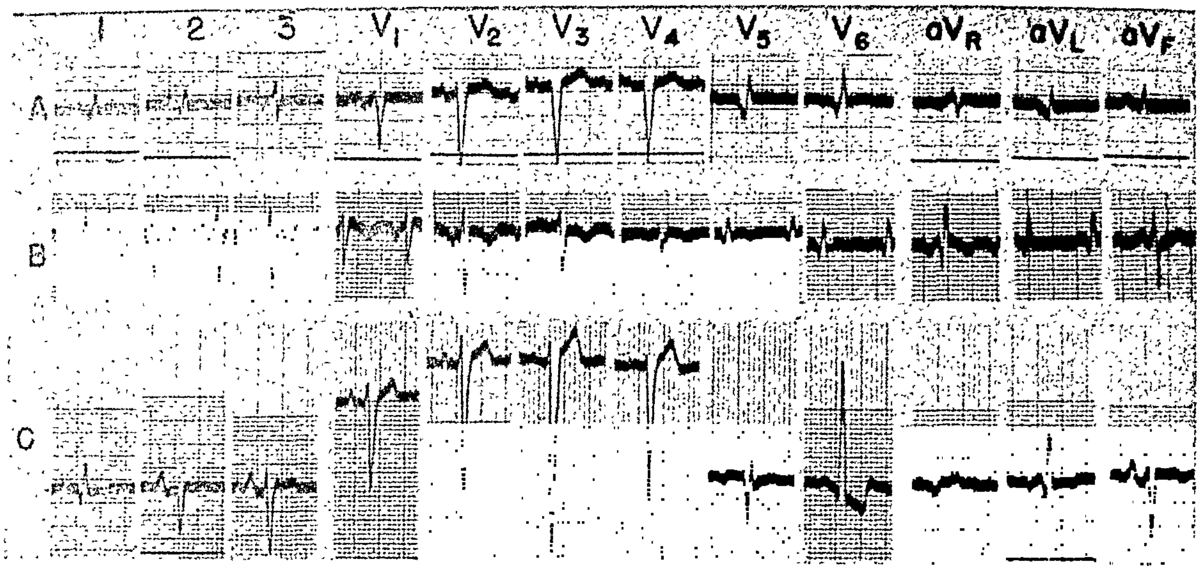

Fig. 13.—Old anterolateral infarction. *A*, Case 43; *B*, Case 44; *C*, Case 45.

Fig. 14.—Roentgenogram of injected heart of Case 44.

Electrocardiographic Findings.—An electrocardiogram obtained on the seventh hospital day, while the patient was receiving maintenance doses of digitalis, is reproduced in Fig. 13,*C*. The initial R showed the expected increase in amplitude as the electrode was moved from Position 1 to 2 and then a progressive paradoxical decrease at Positions 3 and 4. In view of these findings, the deep Q in Lead V_5 was diagnostic of infarction of the anterolateral aspect of the apex. The minute Q and tall succeeding R wave in Lead V_6 were compatible with left ventricular hypertrophy and were not diagnostic of infarction. The contour of the depressed RS-T segment in this lead was typical of digitalis effect. The findings in Lead aV_R suggested backward rotation of the apex and when considered along with the inverted P wave in aV_L, suggested that the abnormal QR pattern in aV_L was more likely transmitted from the posterolateral than from the anterolateral wall of the left ventricle. The infarct was considered old and healed because of the absence of significant changes in serial electrocardiograms. Standard Lead I showed an abnormal QR typical of anterolateral infarction. The initial R wave of Lead aV_F was not carried over into Lead II because of cancellation by a simultaneous positive potential of equal magnitude referred to the right arm, as will be appreciated by comparison of the initial upward deflections of aV_R and aV_F.

Pathologic Findings.—The heart weighed 504 grams as a result of left ventricular hypertrophy. There was an old, patchy infarct of the anteroseptal and anterolateral aspect of the apex, occupying essentially the same position in the first two segments as that in Case 21 (Fig. 2), but smaller and more sparse in the third segment. This was apparently responsible for the decreasing R wave in Leads V_3 and V_4 and for the abnormal Q wave in V_5. In addition, there was a separate healed infarct of the apical two-thirds of the posterolateral aspect of the left ventricle. Because of the backward rotation of the heart, it is possible that the abnormal QR pattern in aV_L was transmitted from this rather than from the anterolateral infarct. No evidence of the posterior portion of this infarct was elicited in aV_F, apparently because the potential variations of the right ventricle were referred to the left leg.

CASE 46.—A man, 57 years of age, who had had transient retrosternal oppression and dyspnea on exertion since January, 1945, was first admitted to the hospital on March 25, 1945, in severe congestive failure precipitated by a prolonged attack of retrosternal constriction. Compensation was restored with the aid of digitalization. The patient was fairly comfortable until March, 1947, when angina pectoris and paroxysmal nocturnal dyspnea recurred, followed by congestive failure in May. At this time, signs of an apical cardiac aneurysm were demonstrated by physical and roentgen examination. Compensation was again restored, but cardiac failure recurred after discharge, resulting in death the following month.

Electrocardiographic Findings.—Electrocardiograms which were obtained on April 11, 1945, while the patient was on maintenance doses of digitalis, and exactly two years later, long after the discontinuance of digitalis, are reproduced in Fig. 15,*A*. In the first three precordial leads taken on April 11, 1945, there was an initial upright deflection which was similar in amplitude in Leads V_1 and V_2, but significantly smaller in V_3. The central zonal pattern of Leads V_4 and V_5 was representative of a transmural infarct of the anterolateral wall of the apex, and the marginal zonal pattern of V_6 was taken as evidence of extension of the infarct farther into the lateral wall. Although the ratio of Q to R in Lead aV_L was only 25 per cent, the Q wave in this lead was definitely abnormal because of its coarse notching and broadening and was also indicative of infarction of the subendocardial portion of the lateral wall. The RS-T displacement in Leads V_4, V_5, and V_6 and inversion of the T wave in V_6 and aV_L were referable to the stage of organization. Lead I also showed typical signs of anterolateral infarction. In the tracing made two years later, the main change consisted in a lengthening of the QRS interval from 0.10 second to 0.15 second and the concomitant development of coarse slurring or notching of the QRS in all leads. From a study of the standard leads, it would appear that left bundle branch block had developed. However, the presence of an initial downward deflection in precordial leads over the left ventricle was strongly against this type of conduction defect, since the activation of the septum from right to left, necessitated by left bundle branch block, causes early positivity of the left ventricular cavity and hence an initial upright deflection in all leads facing the left ventricle. The registration of an abnormal Q wave in leads over an infarct of the anterolateral wall of the left ventricle is

possible in the presence of left bundle branch block if the entire septum or the major portion of it is destroyed by infarction. Under these circumstances, early negativity of the right ventricular cavity (resulting from activation of the outer wall of the right ventricle) might be transmitted through the inert septum to the left ventricular cavity, thus initiating the Q wave in left ventricular leads. Increasing negativity of the left ventricular cavity would be expected as the impulse reaches and activates uninfarcted portions of the outer wall of the left ventricle, thereby adding to the Q wave recorded through leads overlying the infarct. Although the combination of left bundle branch block and complete infarction of the septum could not be positively excluded,

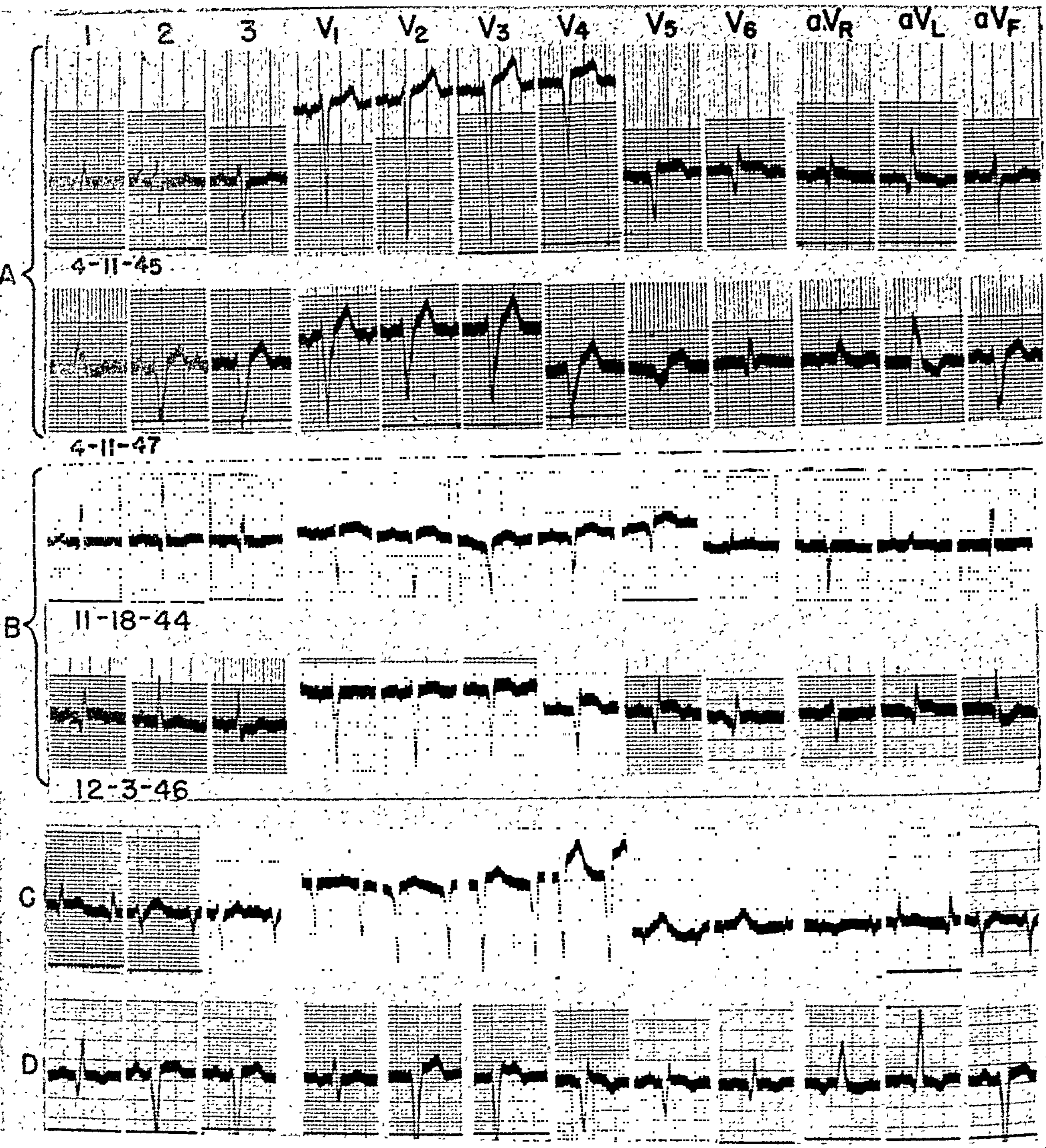

Fig. 15.—Old anterolateral infarction with ventricular aneurysm. *A*, Case 46; *B*, Case 47; *C*, Case 48; *D*, Case 50.

the prominent Q and late intrinsicoid deflection in Leads V_6 and aV_L were more likely an expression of a conduction defect in the lateral wall of the left ventricle. Because of initial negativity of both the right and left arm, the first portion of QRS_1 was isoelectric and the first phase registered in this lead was upright. An initial R was still present in Leads V_1, V_2, and V_3 and the ratio of amplitudes of R and S waves in these leads did not differ significantly from those observed two years previously. Leads V_4 and V_5 still displayed a QS complex, an elevated RS-T junction, and monophasic, upright T wave. The T wave in Lead V_5 was an exact reciprocal of that in aV_L and, like the QS, was representative of cavity potentials transmitted without modification through a completely infarcted anterolateral apical wall. The S wave, which had been added to the QR of Lead V_6, merely indicated that the electrode was not over the last portion of the left ventricle to become activated. The absence of an S wave in aV_L suggested that this lead reflected the potential variations of a more lateral portion of the left ventricle. The development of the conduction defect was in keeping with fibrosis secondary to the healing of an infarct of the subendocardial portion of the lateral wall, and the lack of any significant change in QRS relationships was against extension of the infarct during the two years intervening between the two tracings. Furthermore, several additional electrocardiograms were obtained during the last three months of his life and showed no significant changes in QRS-T, indicating that the tracing of April 11, 1947, was representative of a fixed pattern, as the result of an old infarct of the anterior and lateral aspects of the apex. A high precordial lead taken in the mid-clavicular line at the level of the junction of third intercostal space and sternum revealed a small, M-shaped QRS, and high axillary leads at the same horizontal level resembled Lead aV_L. The disappearance of diagnostic patterns in high leads suggested that the infarct did not involve the basal portion of the anterolateral wall.

Pathologic Findings.—The heart weighed 744 grams and exhibited a large, healed infarct, which caused complete fibrous replacement of the entire circumference of the two apical segments of the left ventricle, as is evident in Fig. 16. The infarct was manifested by dense fibrosis of the subendocardial one-half to three-fourths of the anterolateral wall in the next three segments, corresponding to the areas of avascularity, but spared islands of muscle, chiefly in the subepicardial layer. The infarcted area was the site of a large aneurysm, the apical portion of which was filled with a mural thrombus. The QS complexes, RS-T displacement, and upright T waves in Leads V_4 and V_5 were well correlated with the aneurysm of the anterolateral aspect of the apex. The infarct had converted the septum into a fibrous membrane in the two apical segments and extended into the anterior portion of the left side of the septum in the next three segments, but did not involve the basal one-half of the septum. The limitation of the septal infarction to the apical one-half was strongly against left bundle branch block as a cause of the conduction defect, since the activation of the intact basal one-half from right to left (necessitated by left bundle branch block) should have produced an initial R wave in all leads over the left ventricle. The abnormal Q and very broad, slurred R in Leads V_6 and aV_L could be accounted for by the interspersing of dense patches of fibrosis and islands of intact myocardium in the lateral wall of the left ventricle above the apex. A separate healed intramural infarct situated in the basal one-half of the lateral wall, labelled as *B* in Fig. 16, may have contributed to the abnormalities in V_6 and aV_L. The involvement of the posterior wall was not evident electrocardiographically, probably because of the horizontal position of the heart.

CASE 47.—A woman, 80 years of age, was first hospitalized in March, 1941, because of recent anterior infarct, diagnosed by serial electrocardiograms. Convalescence was uneventful and her heart was fairly well compensated when she was next admitted in November, 1944, because of esophageal diverticulum. She was readmitted moribund in congestive heart failure on Dec. 2, 1946, and died forty-one hours later.

Electrocardiographic Findings.—Electrocardiograms obtained on Nov. 18, 1944, when she was not under the influence of cardiac glycosides, and on Dec. 3, 1946, after the administration of 0.8 mg. of Cedilanid, are reproduced in Fig. 15,*B*. In Lead V_1 of the first tracing there was a distinct initial R, and in Leads V_2 through V_5 there was a QS complex with a notch (R equivalent) near the base of the descending limb of the Q wave. These findings pointed to a large infarct of the anteroseptal and anterolateral wall of the left ventricle, which extended subendocardially into the

lateral wall, as shown by the abnormal QR complex in V_6. In Lead aV_F there was a 2.0 mm. Q wave, which was 25 per cent of the succeeding R. The fact that the borderline Q to R ratio was accompanied by slurring of the ascending limb of the R was interpreted as evidence of extension of the infarct into the subendocardial portion of the posteroapical wall. The RS-T junction was slightly elevated and the T wave upright in all precordial leads. Although the domelike contour in V_6 was suggestive of recent infarct, a fixed residue from the old infarct sustained three and one-half years previously appeared more likely. The standard leads were suggestive of posterior infarction, but gave no positive indication of the large anterolateral infarct. The tracing of Dec. 3,

Fig. 16.—Roentgenogram of the injected heart of Case 46.

1946, showed a distinct initial R in the first two precordial leads, slightly larger in V_1 than in V_2. In view of these findings, the QS pattern in V_3 was significant of a central zone of transmural infarction. Leads V_4, V_5, V_6, and aV_L displayed a QR complex with abnormally deep and prolonged Q wave. Furthermore, the ascending limb of the R wave in Leads V_5 and V_6 was slurred and the time interval from its onset to peak was prolonged to 0.05 second. These findings were typical of the marginal zone of subendocardial infarction, extending into the anterolateral and lateral wall of the left apex. The appearance of a Q in Lead aV_L together with increased RS-T displacement in Leads V_4, V_5, V_6, and aV_L and the classical domelike contour of the RS-T segment suggested that the old infarct had recently extended farther into the anterolateral and

lateral wall of the left ventricle. This diagnosis was supported by the reciprocal depression of the RS-T segment in Leads aV_F and III. The Q wave of Lead aV_L carried over into standard Lead I, producing a pattern typical of anterolateral infarction. The QR complex in Lead aV_F was much like that in the tracing made two years previously. However, the Q wave was cancelled from standard Lead III, because the left arm was more negative than the left leg early in the course of cardiac activation (as shown by the registration of a deeper Q in aV_L than in aV_F). The initially negative potentials of the left arm, which were recorded as a Q wave in aV_L, were registered as an R wave in Lead III, which fused with the upright deflection because of the subsequent positivity of the left leg. Thus, the standard leads of the final tracing were diagnostic of the anterolateral infarct, but gave no evidence of the involvement of the posterior wall.

Pathologic Findings.—The heart weighed 624 grams and exhibited left and secondary right ventricular hypertrophy and an aneurysmal protrusion of the apex. There was a large infarct, causing complete fibrous replacement of the apical segment of the left ventricle and involving the entire circumference in the second segment and the left side of the septum and adjoining subendocardial portion of the anteroseptal wall in the third and fourth segments. The location of the infarct was closely comparable to that in Case 46 (Fig. 16). The infarct was old and healed except in the anterolateral wall of the second segment, where there was microscopic evidence of an old subendocardial infarct and a recent organizing infarct, extending in patchy fashion through the remainder of the wall. Thus, the QS pattern in Lead V_3 and the abnormal QR in V_4, V_5, and V_6 could be correlated satisfactorily with the transmural infarction of the anteroseptal wall and the incomplete transmural infarction of the anterolateral wall of the apex. The electrocardiographic findings suggesting recent lateral extension were borne out at autopsy. The involvement of the posterior portion of the apex was probably responsible for the Q in Lead aV_F. On the other hand, the infarction of the septum was not detected electrocardiographically. It is probable that the R waves in Leads V_1 and V_2 were derived from activation of the hypertrophied right ventricle.

CASE 48.—A man, 62 years of age, was admitted because of left-sided Jacksonian convulsions and left hemiparesis of three weeks' duration. Past history was unobtainable. The association of a diffuse, heaving apical impulse with a faint first sound suggested ventricular aneurysm. Blood pressure was 180/130. No cardiac glycosides were given. Death occurred from pneumonia on the third hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained on the second hospital day is reproduced in Fig. 15,*C*. Auricular fibrillation was present. Leads V_{3R} and V_1 displayed a minute, but distinct initial R wave 0.5 mm. in amplitude. A deep QS complex, coarsely slurred on its descending limb, was present in Leads V_2 through V_4. An abnormal W-shaped complex of low voltage was found in Lead V_5 and a small, but abnormal Q and a minute terminal R were registered in V_6. The ratio of Q to R of 33 per cent in Lead aV_L together with slurring of the Q and prolongation of the upstroke of the R to 0.04 second was abnormal and consistent with a marginal zone of subendocardial infarction. Lead V_7, which is not reproduced, exhibited an R wave of amplitude similar to that in aV_L with coarse notching at its onset in place of the Q recorded in aV_L. The findings in the precordial leads pointed to a very broad central zone of transmural infarction in most of the anterior wall, whereas the findings in V_6 and aV_L were indicative of extension of the infarct subendocardially into the lateral wall. The RS-T take-off was elevated 2.0 mm. in Lead V_3, 5.0 mm. in V_4, and 1.0 mm. in V_5. The T wave was upright in Leads V_2 through V_7 and in aV_L and the RS-T segment in these leads showed the normal upward concavity. The question arose as to whether the changes in the RS-T segment and T wave were the result of a recent, complete transmural infarction or whether they were a residue of an old, healed infarction. This question was not positively settled electrocardiographically because death occurred before a second tracing could be obtained. The abnormal Q wave in Lead aV_L was carried over into Lead I, producing a pattern diagnostic of anterolateral infarction in this lead.

Pathologic Findings.—The heart weighed 475 grams and exhibited a large aneurysm, which occupied the apical two-thirds of the anterior wall. The wall of this aneurysm was calcified, as evident from the roentgenogram (Fig. 17), and measured only 2.0 mm. in its thinnest portions. The aneurysm was the result of an old, completely healed infarct, which extended into the lateral

wall of the two apical segments and into the septum in the four apical segments. The septal fibrosis continued into the adjoining posterior wall in the two apical segments. The broad central zonal pattern in Leads V_2 through V_5 corresponded closely with the position of the large aneurysm found at autopsy. The elevated, upward concave RS-T segments and upright T waves in Leads V_2 through V_5 were comparable to those in the corresponding leads in Cases 39, 40, and 41 and probably represented cavity potentials derived from repolarization of the hypertrophied posterior and posterolateral walls which were transmitted without modification through the aneurysm to the precordium. It is probable that esophageal leads would have shown a prominent R, depressed RS-T junction, and inverted T reciprocal to the recordings in Leads V_2, V_3, and V_4. Unfortunately, no record was obtained of the potential variations of the posterior wall of the left ventricle in this case, since aV_F displayed an RS complex, presumably transmitted from the right ventricle, due to horizontal position.

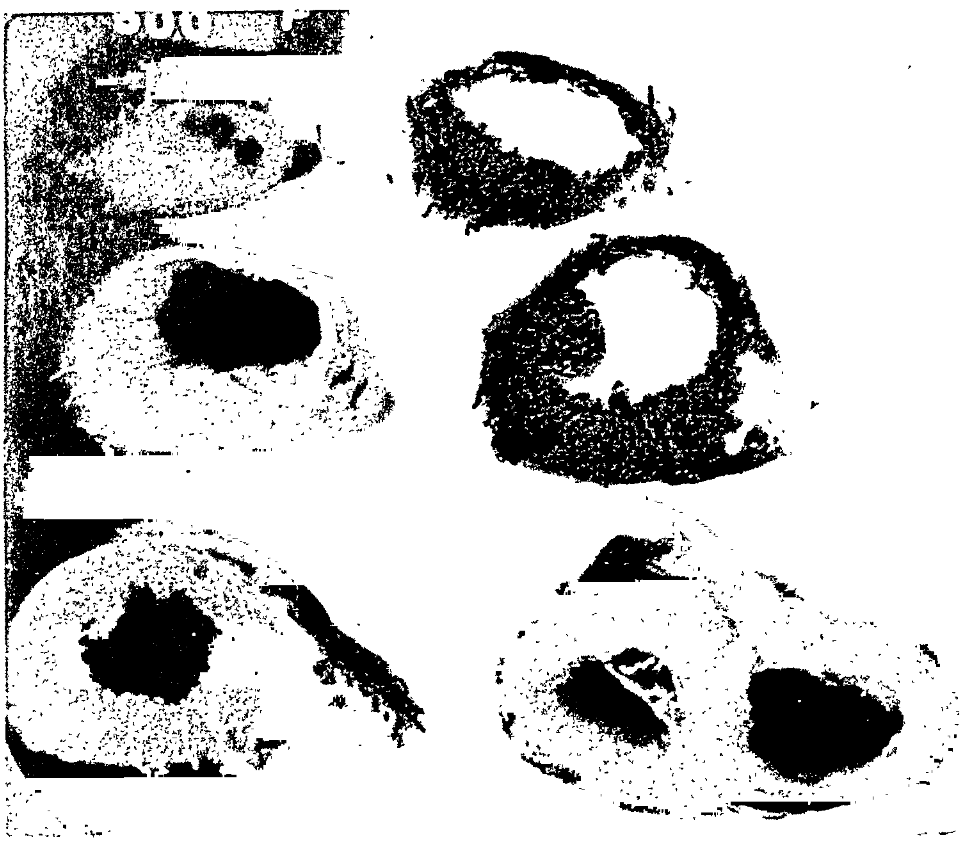

Fig. 17.—Roentgenogram of the injected heart of Case 48, showing a large, calcified ventricular aneurysm.

CASE 49.—A man 63 years of age, moribund, was admitted to the hospital with extreme anasarca due to congestive failure complicated by auricular fibrillation. Past history was unobtainable. Death occurred twenty-three hours later.

Electrocardiographic Findings.—An electrocardiogram taken after administration of 0.8 mg. of Cedilanid is not reproduced because of its close resemblance to that in Case 48 (Fig. 15,*C*). A QS pattern of central zonal type was found in the first five precordial leads and a QR pattern, like that in Lead aV_L, Case 48, was present in V_6. Lead aV_L showed a minute Q, marked slurring of the ascending limb of the R, and increase of time elapsing from onset to peak of R to 0.06 second. From the QRS pattern, a diagnosis was made of a large, transmural anterior infarct, extending into the septum and continuing subendocardially into the lateral wall of the apex. The

RS-T junction was elevated 3.0 mm. in Lead V_3, 4.0 mm. in V_4, and 2.0 mm. in V_5. The contour of the RS-T segments and T waves in the first five precordial leads was much like that in Leads V_3 and V_4 of the tracing of July 6 in Fig. 11,*C*. The changes were ascribed to the effects of digitalis superimposed on RS-T displacement secondary to infarction. From a single tracing, a positive differentiation between a recent infarct and a fixed pattern from old infarction could not be made.

Pathologic Findings.—The heart weighed 714 grams as a result of marked left ventricular hypertrophy. There was an old, healed infarct of the apical three-fourths of the anterior aspect of the left ventricle, which extended into the anterior three-fourths of the septum and into the apical one-third of the lateral aspect of the left ventricle. This infarct was comparable in size and position to that in Case 48 except for failure to involve the posterior wall. Microscopic sections showed dense fibrosis, extending through the subendocardial three-fourths of the anterior and lateral walls. There was good correlation between the abnormal pattern in the precordial leads and the extensive infarction of the greater part of the anterior wall and septum and a considerable portion of the lateral wall. The RS-T abnormalities were probably referable in part to the preserved subepicardial layer of muscle and in part to the superimposed effects of digitalis.

CASE 50.—A previously healthy man, 57 years of age, was first admitted on Nov. 8, 1943, because of a paroxysm of painless nocturnal dyspnea, proved electrocardiographically to have been due to recent anterolateral infarction. On Jan. 17, 1944, he was seized with precordial pain, radiating to the left shoulder, due to an extension of his infarct farther into the lateral wall, as evidenced by an increase in the Q in Lead V_6 at the expense of the R. A diagnosis of apical aneurysm was later made by physical and roentgen examination. Serial electrocardiograms during the remaining twenty-seven months of his life showed no significant change in QRS pattern. He was fairly comfortable during this period except for a second severe paroxysm of nocturnal dyspnea on Oct. 29, 1945, which resulted in hospitalization, and a third attack in April, 1946, which caused death.

Electrocardiographic Findings.—An electrocardiogram, illustrated in Fig. 15,*D*, was obtained on Dec. 5, 1945, after stabilization of the QRS-T pattern and while the patient was taking maintenance doses of digitalis. Lead V_1 displayed a minute Q wave 1.0 mm. in depth, an R wave 4.0 mm. tall, and a slightly larger S wave. An initial Q preceding an RS complex is abnormal in Lead V_1 and may have been due to activation of the septum from right to left, as a result of septal infarction. Because of the abnormally large amplitude of R in proportion to that of S in Lead V_1, right ventricular hypertrophy was regarded as a possible alternative explanation for the QR pattern in Lead V_1. In view of the findings in Lead V_1, the QS complex in V_2 and V_3 was significant of central zone of infarction, occupying the anteroseptal portion of the left ventricle. The deep, broad initial downward component of the QR complex of Leads V_4, V_5, and V_6 pointed to infarction, extending from the endocardial surface through the greater part of the anterolateral wall of the left ventricle. Although the Q to R ratio in aV_L was only about 12 per cent, the broadening of the Q wave and the slurring and prolongation of the ascending limb of the succeeding R were abnormal and also pointed to infarction of the subendocardial portion of the lateral wall. Lead aV_R displayed an unusually tall, slurred R, probably derived from the posterobasal aspect of the left ventricle. The fact that this would be recorded as a downward deflection in Lead I accounts for the exceptionally deep Q wave in this lead. From the contour of the RS-T segment in Leads V_3 through V_6, one might surmise that the infarct was in the stage of organization; however, this pattern had become fixed prior to this tracing and remained so during four subsequent months of observation. Therefore, an electrocardiographic diagnosis was made of a large, transmural anteroseptal infarct, continuing into the interventricular septum and extending subendocardially into the lateral wall of the left ventricle.

Pathologic Findings.—The heart weighed 570 grams and exhibited a large, completely healed infarct, which involved the entire circumference of the left ventricle in the apical two segments and the anteroseptal wall and septum in the next three segments and extended for a short distance across the septum into the anterior wall of the right ventricle. The apical one-half of the anteroseptal wall of the left ventricle and the entire circumference of the apex were reduced to a thickness of 2.0 to 3.0 mm., as a result of complete fibrous replacement and aneurysm formation. The

position of the aneurysm and infarct was identical with that of Case 46 (Fig. 16), except that this lesion did not extend into the lateral wall above the second segment. The initial Q in Lead V_1 was most likely secondary to the extensive lesion of the septum, but might have been due in part to the small extension into the anterior wall of the right ventricle. The large aneurysm was probably responsible for the QS complex in Leads V_2 and V_3 and should have been manifested by a QS complex in V_4 and V_5 as well. The source of the late R waves in Leads V_4 and V_5 is obscure. This case also constitutes another example of cardiac aneurysm with fixation of the RS-T segment and T waves in a pattern resembling that encountered during the process of organization of a recent infarct.

COMMENT

Correlation Between the Leads Exhibiting QRS Abnormalities and the Location of the Lesions of the Anterior and Lateral Walls at Autopsy.—This has been discussed in detail in each individual case report, but remains for summary. When the infarct is confined to the anteroseptal portion of the free wall of the left ventricle, abnormal QS or QR complexes are limited to one or more of the first four precordial leads.[12] When an anterior infarct continues into the lateral aspect of the apex, diagnostic QRS abnormalities are found not only in one or more of the first four precordial leads, but also in Leads V_5, V_6, and/or aV_L.

The findings in the first four precordial leads are, in general, comparable with those produced by an infarct limited to the anteroseptal wall of the left ventricle. An abnormal initial downward deflection in right ventricular Leads V_1 and V_2 may occur as a manifestation of extension of the infarct into the septum. An abnormal QS in Lead V_2 was also observed in association with an infarct involving the apical one-half of the anterior wall, but not extending into the septum, as in Case 28. The lesion of the anterior wall was characteristically manifested by QRS abnormalities in Leads V_3 and V_4. The incidence of a QS in both V_3 and V_4 was distinctly greater in this series than in the group of infarcts confined to the anteroseptal wall of the left ventricle. A QS deflection was found in both Leads V_3 and V_4 in association with infarction limited to the apical one-third, as well as with much more extensive lesions. A positive distinction between infarcts confined to the apical one-third and those involving the apical two-thirds or more of the anterior wall could not be made from the six customary precordial leads. An infarct of given size tended to produce QRS abnormalities in a greater number of leads when thorax and heart were small than when large. Hence, there was a tendency to overestimate the size of infarcts in persons with narrow chests and to underestimate the size in persons with broad chests.

The QRS pattern in Leads V_5, V_6, and aV_L served to differentiate an anterior infarct extending into the lateral aspect of the apex from those limited to the septal wall. The findings in these leads have been correlated with those at autopsy in fifty-seven cases exhibiting a large anterior infarct extending into the apical one-third or more of the lateral wall (Cases 20 through 54, 56 through 59, 61, 62, 64 through 66, 69, 71, 72, 74, 77 through 80, 82, 96, and 151 through 153). An abnormal QS or QR complex was found in all three leads in twenty-seven cases, in Lead V_5 and in either V_6 or aV_L in fifteen cases, in V_5 alone in eight, and in aV_L alone in two. In several of the cases where diagnostic QRS abnormalities were present in only one or two of the three leads, borderline findings were

obtained in the remaining leads. There was no direct relation between the number of leads showing diagnostic QRS abnormalities and the extent of the involvement of the lateral wall at autopsy, since there were a number of cases in which an abnormal QR or QS pattern was found in all three leads (V_5, V_6, and aV_L) in association with an infarct confined to the apical one-third of the lateral wall, whereas there were others in which QRS abnormalities appeared in only one or two of these leads, despite the presence of infarction in the apical one-half of the lateral wall. There were five cases in which definitely abnormal QR or QS complexes were not found in either Lead V_5, V_6, or aV_L (Cases 35, 36, 38, 56, 82). A detailed discussion of each of these cases will be given later.

Correlation of the QRS-T Pattern in the Precordial Leads With the Distribution of the Infarct Between Endocardium and Epicardium.—The infarct involved the apical one-third or more of the anteroseptal and lateral walls in fifty-six cases and the middle one-half of the anteroseptal and lateral walls in one case. The anteroseptal portion of the infarct was transmural in thirty-eight cases and was confined to the subendocardial one-fourth to three-fourths in the other nineteen. In eight of these, the subendocardial one-half to three-fourths of the anteroseptal wall was infarcted, and in eleven only the subendocardial one-fourth to one-half was involved. Although the anteroseptal portion of the infarct was transmural in thirty-eight, the extension into the lateral wall was confined to the subendocardial layer in fourteen of these, leaving twenty-four cases with transmural infarction of all or part of the apical one-third of the lateral wall. The transmural extension into the lateral wall reached or closely approached its junction with the posterior wall in fourteen cases and was limited to the anterior one-half or less of the apical aspect of the lateral wall in the other ten. The lateral portion of the infarct was confined to the subendocardial one-fourth to three-fourths of the wall in the remaining thirty-three cases and involved more than the anterior one-half of the apical aspect of the lateral wall in twenty-four of these and less than this in nine.

QRS Pattern in Transmural Infarction.—There was excellent correlation between the QRS pattern in Leads V_3 and V_4 and the pathologic findings in twenty-nine of the thirty-eight cases with transmural infarction of the anteroseptal wall. A smooth or notched QS complex was recorded in both Leads V_3 and V_4 in nineteen of these and in either V_3 or V_4 in the other ten. An abnormal QR pattern, characterized by a Q wave which exceeded 0.02 second in duration from onset to nadir and amounted to 25 per cent or more of the amplitude of the succeeding R, was found in these leads in Cases 80, 50, and 72. The terminal R in Case 80 could be correlated with patches of preserved muscle in the subepicardial layer. The small late R in V_3 and V_4 in Case 50 was more difficult to explain, since the apical one-half of the anterior wall was completely replaced by fibrous tissue. The upstroke may have been derived from intact muscle in the basal portion of the anterior wall. The findings in Case 72 were unusual and will be discussed in detail later along with those in the remaining six cases (Cases 34, 35, 36, 45, 56, 77), where an initial R rather than a Q was found in precordial leads over the infarct.

There was satisfactory correlation between the QRS pattern in Leads V_5 and V_6 and the pathologic findings in twelve of the twenty-four cases of transmural infarction of the lateral wall. A smooth or notched QS was found in both Leads V_5 and V_6 in three and in V_5 alone in nine of these cases. The rarity of a QS complex in V_6 can be explained by the fact that the transmural lesion rarely occupies more than the apical one-third of the lateral wall. Activation of uninfarcted portions of the lateral wall presumably gave rise to an R wave following the initial downstroke. An abnormal QR complex was recorded in both V_5 and V_6 in five cases and in V_5 alone in three cases. The late R wave was probably derived from portions of the lateral wall beyond the border of the lesion, but might have been accounted for in some of the cases by preserved muscle found within the infarct. Four of the patients in whom transmural infarction of the anteroseptal wall was accompanied by an initial R in Leads V_3 and V_4 also displayed an initial upstroke in V_5 and V_6 in association with transmural infarction of the lateral wall (Cases 34, 35, 36, 77).

RS-T Pattern in Recent Transmural Infarction.—The QS complexes associated with recent transmural infarction were usually accompanied by abnormal elevation of the RS-T junction and by straightening or upward convexity of the RS-T segment. The associated T waves were at first monophasic and upright, as exemplified by Leads V_3 and V_4 in Case 24 (Fig. 3,*C*), and subsequently underwent a progressive cove-like inversion, as described and illustrated elsewhere.[12] The QS and RS-T complexes were comparable to those registered through epicardial leads in animals with infarcts which have extended from endocardium to epicardium, but have not completely destroyed the subepicardial muscle.[14] Although the QS complex was representative of a transmural lesion, the RS-T contour indicated the presence of subepicardial muscle that was injured, but not dead. Similar RS-T and T-wave patterns are observed in animals with injury localized to the subepicardial layer and in human pericarditis, and are differentiated from the RS-T and T-wave patterns of myocardial infarction by the fact that they are associated with essentially normal QRS complexes.

The QS complexes overlying areas of recent transmural infarction in Cases 39, 40, and 41 were accompanied by only slight RS-T elevation and an upwardly concave RS-T segment and upright T wave, which exhibited no significant change in serial tracings over periods of six days, five days, and two days, respectively. The QRS-T complex in the first four precordial leads in Case 39 was an almost exact reciprocal of that in Lead aV_F, which reflected the potential variations of the uninfarcted diaphragmatic wall of the left ventricle. In some animals with experimental infarcts, a comparable QS deflection, elevated concave RS-T segment, and upright T wave were consistently recorded in repeated tracings through overlying epicardial leads. These findings were almost identical with those obtained through a lead from the ventricular cavity and were reciprocal to those registered through a direct lead from the epicardium of the opposite normal wall.[14] The similarity of both the QRS and RS-T complexes in epicardial leads to those in cavity leads indicated that the intervening muscle was completely dead and contributed no electromotive force, but merely served as a

conducting window for the transmission of cavity potentials to the surface. These deductions were supported by the autopsy findings, which revealed complete destruction of all muscle in the subjacent wall.

Thus, central zonal patterns associated with recent transmural infarction may be classified into two types, according to the contour of the RS-T segment: (1) QS followed by abnormal RS-T elevation and a straightened or upwardly convex RS-T segment, which undergoes characteristic changes in serial tracings; (2) QS followed by slight RS-T elevation, an upwardly concave RS-T segment, and upright T wave, which tends to remain constant in serial tracings.

QRS Pattern in Subendocardial Infarction.—Isolated cases have been reported[16,17] of recent infarction of the subendocardial portion of the anterolateral wall, manifested by preservation of the initial R waves and acute RS-T depression in Leads I and IVF. If a sufficient number of precordial leads are taken, an abnormal QR complex or a very coarsely notched QS deflection should be demonstrable. Patterns of this type were recorded in Leads V_3 and V_4 in eleven of the nineteen patients with infarction of the subendocardial one-fourth to three-fourths of the anteroseptal wall and corresponded closely with the pathologic findings. A QS with smooth or slightly slurred or notched ascending and descending limbs was registered in Cases 49, 57, 66, and 151, despite the fact that the infarct did not extend through the entire wall. The discrepancy between electrocardiographic and autopsy findings was not great in Cases 49 and 57, since the infarct extended through the subendocardial three-fourths and two-thirds of the walls, respectively, in these cases. An infarct limited to the subendocardial one-half of the wall in Case 151 was manifested by a splintered QS in Lead V_4. A smooth QS recorded in V_3 and V_4 in Case 66 could not be correlated with the fact that the infarct of the free portion of the anteroseptal wall was confined to the subendocardial one-fourth. However, the infarct in this case also involved the greater part of the left side of the septum. This gave rise to diagnostic signs in Leads V_1 and V_2 and probably was also responsible for the QS deflection in V_3 and V_4, as a result of displacement of the transitional zone to the left. Four cases of subendocardial anterior infarct (Cases 38, 44, 51, 82) remained, in which Leads V_3 and V_4 displayed an atypical finding, namely, an initial R wave. These will be discussed along with the six cases of transmural anterior infarct in which an initial upstroke was found in Leads V_3 and V_4.

There was good correlation between the QRS pattern in Leads V_5 and V_6 and the pathologic findings in twenty-seven of the thirty-three cases of infarction of the subendocardial one-fourth to three-fourths of the apical one-third or more of the lateral wall. An abnormal QR pattern was recorded in Lead V_5 or in V_5 and V_6 in twenty-six of these and a W-shaped QRS was registered in the other case. The remaining cases require individual discussion. The original tracing of Case 53 showed a smooth QS complex in both Leads V_5 and V_6, but a subsequent tracing showed a QR complex in these leads, which corresponded closely with the infarct of the subendocardial two-thirds of the apical portion of the lateral wall found at autopsy. The experience with this case merely illustrates the fact that a QS complex may be recorded early in the course of infarction, even though the subjacent myocardium is not entirely dead. With recovery of the

subepicardial layer, a late R wave may appear. The infarct in Case 31 was transmural in the anterior wall and became subendocardial in the lateral wall. The QS complex recorded in Lead V_5, as well as those in V_3 and V_4, was probably referable to the lesion of the anterior wall, and the QR complex of Lead V_6 conformed to the lesion of the lateral wall. A QS complex was found in Leads V_3, V_4, and V_5 of Case 49 in association with infarction of the subendocardial three-fourths of the anterolateral wall. A serious discrepancy between the QRS pattern in Leads V_5 and V_6 and the infarction of the subendocardial portion of the lateral wall was encountered in only three cases (Cases 38, 56, 82), where an initial R wave was recorded in both leads. These cases are discussed later.

RS-T Pattern in Recent Subendocardial Infarction.—Experimental injury localized to the subendocardial layer causes acute RS-T depression in overlying leads.[18] Acute coronary insufficiency characteristically produces transitory ischemia and injury of the subendocardial layer, manifested by transient RS-T depression in left ventricular leads, as exemplified by Case 38. In sixteen cases of this series, autopsy disclosed recent or organizing infarction, which appeared to be confined to the subendocardial portion of the anterolateral or lateral wall of the left apex. Precordial leads overlying the subendocardial lesion revealed abnormal RS-T depression in three cases, isoelectric RS-T junction with cove inversion of the T wave in three cases, and elevation of the RS-T junction and upward convexity of the RS-T segment in ten cases. The degree of upward displacement of the RS-T segment in these ten cases was not as great as that found in most transmural lesions, but the contour of the RS-T segment and T wave resembled that resulting from localized lesions of the subepicardial layer. Injury to this layer was therefore postulated, despite the apparent limitation of the infarct to the subendocardial one-third to two-thirds of the wall. In the three patients with isoelectric RS-T junction and cove inversion of the T wave, the infarct was in the process of organization and had apparently progressed beyond the stage of injury.[19]

Causes of an Initial R in the Last Four Precordial Leads in the Presence of a Large Subendocardial or Transmural Anterolateral Infarct.—The registration of an initial R in Leads V_3 and V_4 in the presence of a transmural or subendocardial infarct of the apical one-third or more of the free anteroseptal wall of the left ventricle is a very atypical finding, but was encountered in ten of the fifty-seven cases (Cases 34, 35, 36, 38, 44, 45, 51, 56, 77, 82). An initial upstroke in Leads V_5 and V_6 is likewise a very atypical finding in the presence of a transmural or subendocardial infarct of the apical one-third or more of the lateral wall, but was encountered in seven of the foregoing cases (Cases 34, 35, 36, 38, 56, 77, 82). These cases collectively exemplify the usual causes for difficulty or failure in the diagnosis of large anterolateral infarcts from the precordial electrocardiogram, and therefore will be discussed in detail. The causes for the registration of an initial R rather than a Q in Leads V_3 and V_4 in the presence of a subendocardial or transmural infarct of the anteroseptal portion of the apex and for a similar finding in V_5 and V_6 in the presence of a comparable lesion in the lateral aspect of the apex may be classified as follows:

1. *Displacement of the transitional zone to the left* may occur as a result of (a) shift of the entire heart farther into the left side of the thorax secondary to intrathoracic disease, (b) right ventricular dilatation, (c) clockwise rotation of the heart about its anteroposterior and longitudinal axes, (d) marked backward rotation of the apex about the transverse axis of the heart, and (e) various combinations of the foregoing factors. When the transitional zone is displaced to the vicinity of the anterior axillary line, the first four precordial leads will reflect principally the potential variations of the right ventricle and right side of the septum. Hence, an RS pattern like that normally found in Leads V_1 and V_2 may be recorded in V_3 and V_4 in the presence of infarction of the anteroseptal wall of the left ventricle, as illustrated by Case 44. Furthermore, under these circumstances, an anteroseptal infarct which does not extend into the lateral wall may be manifested by an abnormal QS or QR complex in Leads V_5 and V_6, but not in V_3 and V_4, as will be exemplified by Cases 67 and 68, to be reported in the next communication. Rarely, the transitional zone may be displaced into mid-axilla or beyond. Under these circumstances, signs of an extensive infarct of the anterolateral wall of the left ventricle may not be referred to any of the six customary precordial leads, as exemplified by Case 72. The first five precordial leads and aV_L in this case displayed a similar Q, late R, and simultaneous intrinsicoid deflection. These findings indicated that all of these leads reflected the potential variations of the right ventricle and the right side of the septum and could be correlated directly with the dilatation of the right ventricle and infarction of the septum found at autopsy. Since Lead V_6 showed a transitional complex, V_7 and V_8 would have been needed in this case for exploration of the anterolateral wall of the left ventricle and for the ante-mortem detection of the extensive infarction found in this region at autopsy.

2. *Left bundle branch block* was present in Case 82 and completely obscured an old, healed infarct of the subendocardial one-half of the anterolateral wall. Activation of the septum from right to left, necessitated by the conduction defect, caused early positivity of the left ventricular cavity and thus an initial upward deflection in all precordial leads facing the left ventricle. This prevented the registration of a Q wave through precordial leads overlying the anterolateral infarct and thus accounted for the failure of the electrocardiogram to reveal diagnostic signs. When left bundle branch block occurs as a result of extensive infarction of the septum, the destroyed septum may contribute no electromotive force and may merely transmit the negative potentials developing early in the right ventricular cavity (as a result of activation of the outer wall of the right ventricle) to the left ventricular cavity, thereby permitting the registration of a Q wave in precordial leads over an anterolateral infarct.[20]

3. *Registration of the electrocardiogram soon after the onset of symptoms and before the myocardial changes have progressed to the point of obliteration of the response to the activating impulse.* Significant RS-T displacement without QRS abnormalities is a familiar finding in spontaneous or induced angina pectoris and might be expected in electrocardiograms obtained shortly after the onset of attacks that eventuate in myocardial infarction. For example, abnormal

RS-T depression, typical of acute subendocardial injury, without significant alteration in the QRS, was found in an electrocardiogram obtained two and one-half hours after the onset of an attack in Case 38 and completely disappeared the following day. Death occurred in a second attack six days later and autopsy revealed a very early ringlike infarct, involving the subendocardial one-half of the entire circumference of the left ventricle. If the age of the lesion was correctly estimated from the microscopic sections, all electrocardiograms were obtained prior to the onset of the infarct. Hence, this case should probably not be classed among those characterized by failure in the development of a diagnostic QRS pattern in Leads V_5, V_6, or aV_L. Nevertheless, an infarct evenly distributed throughout the subendocardial one-half of the entire circumference of the left ventricle[21] might be expected to cause abnormal reduction in the R wave without abnormal Q waves in left ventricular leads.

Significant RS-T displacement without an abnormal QR or QS complex might be expected in electrocardiograms obtained early in the course of an attack that ends in myocardial infarction, since the onset of symptoms probably antedates the development of histochemical changes responsible for the QRS abnormalities by a variable period. Marked RS-T elevation has been demonstrated within sixty to ninety seconds after coronary ligation in animals,[22] whereas the development of abnormal initial downward deflection is delayed for minutes or hours.[23]

An electrocardiogram obtained four hours after the onset of the pain in Case 77 showed extreme RS-T elevation in Leads V_3, V_4, and V_5 associated with a broad initial R wave of normal voltage. At death, eleven hours later, a very early transmural anterolateral infarct was found. The registration of a broad R instead of a Q in the precordial leads may have been due to an acute injury at a stage which slowed, but did not abolish, activation of the anterolateral wall. An electrocardiogram taken eight hours after the onset of the pain in Case 36 displayed typical RS-T elevation in Leads V_4 and aV_L, but merely showed an abnormally small initial R in V_4, V_5, and V_6 and a minute QR in aV_L too low in voltage to be diagnostic of lateral infarction. At death, fifty-eight hours later, recent transmural infarction of the apical portion of the anterior and lateral walls was found. The findings in this case were best explained by the assumption that the lesion, at the time of the electrocardiogram, had reduced, but not completely obliterated, the myocardial response to the activating impulse. This hypothesis was not adequately tested in these cases, because of failure to obtain a second electrocardiogram, but was strongly supported by the findings in Case 139, to be reported in detail later. The first electrocardiogram, taken four and one-half hours after the onset of the pain in Case 139, showed marked RS-T displacement with normal R waves in Leads V_4, V_5, and V_6, whereas a second electrocardiogram, taken forty-four hours later, showed significant reduction in the initial R of Leads V_4 and V_6 and a QR complex in V_5 that conformed closely with the localized anterolateral infarct found at autopsy. The experience with these cases emphasizes the importance of obtaining further electrocardiograms when the original tracing, taken soon after the onset of symptoms, is inconclusive.

4. *Patchy infarction with preserved islands of muscle in the subendocardial layer or scattered through the wall.* An initial upstroke may be present in precordial leads over lesions of this type,[24] particularly when there is coexistent infarction of the greater portion of the posterior wall. The registration of a QS or an abnormally reduced R in precordial leads over an incompletely infarcted wall probably depends, in part, upon the magnitude of the negative potentials which build up in the left ventricular cavity during activation of the intact portion of the wall. These negative cavity potentials are available for transmission to the precordium through the dead portions of the infarcted wall and thus might be expected to oppose positive potentials referred to the precordium during activation of intact remnants of muscle within the infarct. When the infarct is confined to the anterolateral wall, the relatively great negative potentials developing in the cavity, as the result of activation of the intact posterior wall, tend to obliterate the relatively weak positive potentials developed from activation of remnants of muscle within the infarct, thereby leading to the registration of a QS complex in overlying precordial leads. When most of the posterior wall is likewise infarcted, the negative cavity potentials may be sufficiently reduced so that they fail to counteract even the weak positive potentials produced by activation of islands of preserved muscle in the infarct. This was regarded as the most likely explanation for the small initial R waves recorded in Leads V_3 through V_6 in Case 35 and for those recorded in Leads V_3 and V_4 in Cases 45 and 51.

5. *Localized complete transmural anterolateral infarction complicated by extensive infarction elsewhere in the left ventricle.* In Case 56 small initial R waves were found in leads from the precordium, covering a ventricular aneurysm consisting exclusively of fibrous tissue. Since precordial leads over the aneurysm subtended portions of intact myocardium beyond the boundaries of the aneurysm, positive potentials developing during activation of the surrounding myocardium could have been transmitted to the electrode over the aneurysm. At the onset of ventricular activation, the magnitude of these potentials at the precordial surface over the aneurysm was apparently greater than that of negative potentials transmitted through the cavity in the aneurysmal wall, as a result of the marked reduction in the latter potentials due to a coexistent infarction of the apical one-half of the septum and lateral wall and most of the posterior wall.

6. *Infarction of the left side of the septum,* in the absence of left bundle branch block, may cause local delay in passage of the impulse and thus indirectly favor activation of intact remnants of septal muscle by impulses distributed through the Purkinje plexus of the right side of the septum. Activation of the septum by impulses passing from right to left causes early positivity of the left ventricular cavity and thus an initial R in precordial leads overlying an infarct of the anterior wall of the left ventricle. This mechanism was believed responsible for the minute initial R in the precordial leads in Case 34.

Estimation of the Age of the Infarct From the Electrocardiogram.—The finding of a characteristic abnormality in the QRS complex is indicative of the presence of infarction, but gives no clue as to the age of the lesion. A significant increase in

the degree of QRS abnormality in one or more leads of serial tracings, as in Cases 21 and 42, may be construed as evidence of extension of the infarct, or a significant decrease may be attributed to recovery of damaged muscle consequent upon healing, provided one can be reasonably certain of a constant position of the electrode in reference to the heart.

Estimation of the age of the lesion is generally based chiefly on the RS-T and T-wave patterns. Positive conclusions are not justifiable from the examination of a single electrocardiogram without other clinical data, because of the fact that an elevated, domelike, monophasic, upright RS-T segment and T wave or cove inversion of the T wave, identical with that found during recent infarction, may persist indefinitely as a fixed residue. This is especially prone to occur when there is extensive destruction and fibrous replacement of the wall, sufficient to lead to a ventricular aneurysm,[7] as illustrated by the four patients whose tracings are reproduced in Fig. 15. The abnormal RS-T segments and T waves probably represented cavity potentials transmitted through the aneurysm without modification when the wall was completely replaced by fibrous tissue or transmitted with slight alteration when it contained muscle remnants capable of activation and repolarization. A presumptive diagnosis of recent infarction might have been made from the examination of a single electrocardiogram in any of these four cases, and demonstration of the absence of significant change in serial tracings would have been necessary to prove the presence of old, rather than recent infarction.

Serial tracings during recent transmural infarction generally show the familiar RS-T evolution, consisting essentially of marked elevation of RS-T junction and domelike, monophasic, upright RS-T complex at the beginning, followed by progressive return of RS-T junction toward the isoelectric line, accompanied by deepening covelike inversion of the T wave. These changes are observed when muscle in the subepicardial layer is acutely injured, but not dead. In serial tracings during recent transmural infarction, the QS complexes are occasionally accompanied by a constant RS-T and T-wave pattern, characterized by slight elevation of the junction, an upward concave segment, and an upright T wave. These findings may occur as a manifestation of complete destruction of the subjacent wall and are presumably due to transmission of cavity potentials through the infarcted wall without modification, not only during ventricular activation, but also during repolarization. Although such findings are usually the result of an old, healed transmural infarction, their occasional association with a recent complete transmural infarct makes consideration of the clinical data essential in the differential diagnosis.

QRS and RS-T abnormalities resembling those of recent infarction may occur in serial tracings as a result of (1) old, healed infarction complicated by an acute, but independent, pericarditis, as in Case 28; (2) old, healed infarction with superimposed effects of cardiac glycosides. The effects of digitalis on the RS-T segment and T wave depend upon the direction of the major phase of the QRS. In leads with a QS complex and upright T wave, full digitalization may result in further elevation of the RS-T junction or straightening or upward convexity of the segment and increased amplitude of the T wave, as in Lead V_4

of Case 42. This can be recognized as a digitalis effect by the shortening of the QT interval and by the presence of the characteristic depression of the RS-T segment and inversion of the T wave in leads with prominent R waves.

Value of the Standard Limb Leads in the Detection of Large Anterolateral Infarcts.—Among the fifty-seven cases of infarction involving the apical one-third or more of the anterior and lateral walls of the left ventricle, there were thirty-one in which the standard limb leads were not diagnostic nor strongly suggestive of anterolateral infarction. The findings in these leads were interpreted as indicating left ventricular hypertrophy in seven of these and nonspecific abnormalities, including right or left bundle branch block, in fifteen. In the other nine cases the standard leads were diagnostic or suggestive of an associated posterior infarct, but not of the anterolateral lesion. Thus, the standard leads are of limited value even for the recognition of large anterolateral infarcts.

SUMMARY

The findings in the Wilson precordial leads and in the standard and Goldberger limb leads have been analyzed and correlated with the pathologic findings in fifty-seven cases of infarction of the apical one-third or more of the anterior and lateral walls of the left ventricle. The infarct was distributed transmurally through the apical one-third or more of both the anteroseptal and lateral walls in twenty-four cases; it was transmural in the anteroseptal wall and subendocardial in the lateral wall in fourteen cases; and was confined to the subendocardial one-fourth to three-fourths of both the anteroseptal and lateral walls in nineteen cases.

A QS deflection was recorded in Leads V_3 and/or V_4 in twenty-nine of the thirty-eight patients with transmural infarction of the apical one-third or more of the anteroseptal wall of the left ventricle and corresponded closely with the findings at autopsy. An abnormal QR complex was present in both leads in three other cases and was explainable by the pathologic findings. Good correlation between a QS deflection in Lead V_5 or in both V_5 and V_6 and transmural infarction of the apical one-third or more of the lateral wall of the left ventricle was obtained in twelve of twenty-four cases and a satisfactory explanation was found for an abnormal QR complex recorded in one or both of these leads in eight other cases.

An abnormal QR or very coarsely notched QS complex was present in Leads V_3 and V_4 in eleven of the nineteen patients with infarction of the subendocardial portion of the anteroseptal aspect of the left apex and conformed closely with the pathologic findings. A smooth or slightly notched QS deflection found in these leads in four additional cases was adequately explained. Good correlation between an abnormal QR pattern in Lead V_5 or in both V_5 and V_6 and infarction of the subendocardial portion of the lateral aspect of the left apex was obtained in twenty-seven of thirty-three cases and a satisfactory explanation was found for a smooth or slightly notched QS complex recorded in one or both of these leads in three other cases.

An initial upstroke was recorded in Leads V_3 and V_4 in ten cases, despite the presence of subendocardial or transmural infarction of the anteroseptal aspect of the left apex, and a similar finding was obtained in Leads V_5 and V_6 in seven of these cases, in spite of a comparable lesion in the lateral wall of the left apex. The causes for the registration of an initial R, rather than a Q, under these circumstances, were as follows: (1) displacement of the transitional zone leftward to the anterior axillary or mid-axillary line; (2) left bundle branch block; (3) infarction of the left side of the septum, necessitating activation of intact septal remnants from right to left; (4) early recording of the electrocardiogram soon after the onset of symptoms and before the myocardial changes have progressed to the point of obliterating the response to the activating impulse; (5) patchy infarction with preserved islands of muscle in the subendocardial layer or scattered through the wall; and (6) extensive infarction of the posterior wall of the left ventricle with consequent reduction in the opposing negative potentials available for transmission through the anterolateral infarct to the precordium.

The QS complexes associated with recent transmural infarction were usually accompanied by abnormal elevation of the RS-T junction and straightening or upward convexity of the segment, followed by progressive covelike inversion of the T wave in serial tracings. This RS-T pattern indicated the presence of subepicardial muscle that was injured, but not dead. In three cases, the QS complexes were accompanied by slight RS-T elevation, upwardly concave RS-T segment, and upright T waves, which exhibited no significant change in a repeat tracing a few days later. These findings were correlated with recent transmural infarction, which had completely destroyed the subjacent myocardium. Recent subendocardial infarcts were generally accompanied by upward displacement of the RS-T segment, less marked in degree, but similar in contour to that customarily found in transmural infarction and attributable to injury to the subepicardial layer. A less common, but more characteristic finding in recent subendocardial infarction consisted in acute RS-T depression, attributable to injury localized to the subendocardial layer. A positive differentiation between recent and healed infarction could not be made from a single electrocardiogram because of the tendency for abnormal RS-T elevation and/or cove inversion of the T wave to remain as a permanent finding in ventricular aneurysm.

The electrocardiograms were taken by Miss Josephine McDonald and were retouched by Miss Evelyn Erickson and Miss Geraldine Chesney.

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AN EXPERIMENTAL STUDY OF ACUTE PULMONARY ARTERIAL OBSTRUCTION, WITH SPECIAL REFERENCE TO THE PRECORDIAL ELECTROCARDIOGRAM

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INTEREST in pulmonary embolism dates from its first description by Virchow in 1846, although White[38] has stated that cases of dyspnea, rapid breathing, and blood spitting had been mentioned as early as 1679. The work of Cohnheim remains as the classic contribution in this field.[24,40] McGinn and White[24] and Barnes[1] were the first authors to describe electrocardiographic changes caused by this disease entity. There is general agreement as to what the standard limb lead electrocardiogram may show in cases of acute pulmonary embolism; however, the frequency of diagnostic changes is rarely stated by the various authors. Apparently this method of diagnosis is used generally only in cases of severe pulmonary embolism or in cases in which the alternative diagnosis of cardiac infarction is considered. Certainly, with the advent of the use of Dicumarol in the treatment of pulmonary embolism, it would be highly desirable to be able to ascertain the time of the occurrence of the first and often undramatic pulmonary embolism in a given case. With this in mind, we investigated multiple "unipolar" precordial leads as well as standard limb leads in dogs in which nonfatal pulmonary embolism had been produced. We were especially interested in studying the incidence of electrocardiographic changes as well as the value of the precordial leads.

McGinn and White,[24] Barnes,[1,2] Sokolow, Katz, and Muscovitz,[34] Currens.[11] Stewart and his co-workers,[35] Durant and associates,[14] Katz and Walsh,[20] and many other authors have contributed to our knowledge of the electrocardiographic changes in acute pulmonary embolism in man. The alterations may consist of: inversion of T_3 (may be cove plane); presence of Q_3 (although the true "Q_3 pattern" of Wilson is not present); the RS-T_2 take-off is usually low (with "staircase ascent"); prominent S_1 (there may be a right axis deviation); and reversal of T_4 over the right precordium. Occasionally a slight widening of the QRS complex is noted, or there may be a slightly low origin of T_1, or a slightly elevated RS-T_3. Currens[11] studied twenty-five selected cases of proved pulmonary embolism in which some electrocardiographic abnormalities were present and he listed the frequency of the various changes. These were

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all patients in whom necropsy was performed not long after the pulmonary embolism. He found inversion of T_3 and reversal of T in CR_2 in twenty-one cases and the presence of S_1 in twenty cases; the presence of a Q_3, RS-T_2 depression, and inversion of the T wave in Lead IV R were somewhat less frequent. The only abnormality was confined to the precordial leads in seven cases and to the limb leads in two cases. (The interpretation of the former is somewhat questionable since previously he stated that inversion of T_3 was present in twenty-one cases.) The foregoing series of thirty cases included only five cases in which recent cardiac infarction as well as acute pulmonary embolism was present. However, coronary occlusion was present in only one of the five cases; presumably, in the other four cases, the concomitant shock was responsible for the coronary insufficiency that produced the cardiac infarction. Some recent experimental work confirming this impression will be mentioned later.[25] Sokolow and his associates[34] noted that evolutions of T, RS-T, or Q did not occur except for an occasional delay in the appearance of Q, or an increase in depression in RS-T_1 or RS-T_2. They found the complete electrocardiographic pattern of McGinn and White[24] in only five of fifty cases of acute pulmonary embolism (necropsy was performed in twenty of the fifty cases). In nine of the cases there were no electrocardiographic changes, but in the remaining cases the electrocardiograms disclosed significant changes, nonspecific abnormalities, disturbances of origin and conduction of impulses, or some of the changes found in cases of myocardial infarction.

Especial interest in the precordial leads has been shown by Wood,[41] Myers and Stofer,[31] Wilson and associates,[39] Barnes,[2] and Katz.[18] According to the last-mentioned author, the precordial electrocardiogram may show a depression of the RS-T segment in Lead CF_5 (with a "staircase ascent") and, characteristically, an inverted T wave in CF_2. He mentioned that in a large percentage of cases of pulmonary embolism, nonspecific changes without diagnostic significance may occur and that all electrocardiographic stigmata disappear within three weeks at the very most, and usually within one day to one week. An exception to this is encountered in an occasional case in which multiple pulmonary emboli occur. Apparently, such emboli produce chronic strain of the right ventricle. Under these circumstances, the electrocardiographic pattern of chronic strain of the right ventricle may persist indefinitely. One of us (A. R. B.) has observed two such cases. Belt[4] reported four cases in which right ventricular hypertrophy was associated with recurrent pulmonary embolism or thromboembolism (post-mortem study); no electrocardiographic studies were mentioned. Myers and Stofer used Wilson's precordial leads of the so-called unipolar type in forty cases of acute strain of the right ventricle (not due to pulmonary embolism in all cases). They found sharply inverted T waves with convex RS-T segments in Leads V_1, V_2, and V_3*; this was most marked in V_1 and least in V_3; therefore, it differed from that found in anteroseptal cardiac infarction. Sokolow and his associates reported slight elevation of RS-T in Lead CF_2 in some of their cases.

*These are unipolar leads introduced by Wilson.

The electrocardiogram made after pneumonectomy in man has been studied by Semisch and Merves[33] and by Barnes.[3] The last-mentioned author did not find significant changes in the electrocardiogram although he followed his patients serially for as long as two weeks in certain instances. He also added that in only three of eleven consecutive cases of definite clinical acute pulmonary embolism did he find typical changes. Semisch and Merves, on the other hand, noted "helpful" electrocardiographic changes in thirteen of fourteen cases in which lobectomy or pneumonectomy had been performed, although in only two cases were the changes "definite." Within twenty-four hours, the electrocardiogram in ten of the cases had reverted to normal. These cases in which pneumonectomy was performed are mentioned only to indicate the amount of pulmonary obstruction necessary to produce electrocardiographic changes in man; it is apparently less than the amount necessary in the dog.[12,15,26,29]

The electrocardiographic changes in the dog caused by acute pulmonary embolism have received attention from many investigators. The nature of these changes is in some dispute. Winans, Goode, and Ashworth,[40] who used ten dogs in which they produced graduated constriction of the pulmonary arteries, noted that most often the earliest and most constant change was a depression of the RS-T_2 take-off (or a downward swing of RS-T_2 ending in an inverted T); RS-T_3 depression and T_2 and T_3 inversion were noted slightly later and less frequently. Further constriction produced irregular terminal changes. Robb and Robb,[32] who used graded constriction of the pulmonary arteries, first noted RS-T depression in Leads II and III. With the last-mentioned changes they noted widening of the base of the right ventricle roentgenographically. Mendlowitz,[30] however, noted elevation of RS-T_2 and RS-T_3 and inversion of T_2 and T_3 in the animals in which he had produced large pulmonary embolism. In one of his animals he did find RS-T_2 and RS-T_3 depression. Most of the animals died or appeared to be near death as a result of the embolism. Love and his co-workers[23] observed some further variations. Much of this variability is thought to be due to the extreme lateral mobility of the dog's heart. Placing and keeping the animal in exactly the same position from day to day does not offer too great an obstacle if the lateral position is used; however, the heart is then in an unnatural position, being thrown to the left or right side of the thorax. The variability of the standard lead electrocardiogram has been well brought out in the work of Betlach.[5] He especially noted the almost complete unpredictability of the T waves. Katz, Soskin, and Frisch[19] and Lalich, Cohen, and Walker[21] also made original contributions that supported the finding of great variability of the electrocardiogram of the dog.

By using needle electrodes and following Lead II serially, Cabitt, Altschule, and Zamcheck[9] observed reversal of the T wave in all of eleven dogs that had undergone unilateral pneumonectomy (whether control was positive or negative). They also observed transient cardiac arrhythmia in five of the animals. Most other investigators claim that much greater pulmonary arterial occlusion must be obtained to produce electrocardiographic changes; in most cases, enough occlusion to produce right ventricular dilatation must be present. Special interest in the dynamics of experimental acute obstruction of the pul-

monary artery has been shown by many investigators.[15,28,29,37] Malinow, Katz, and Kondo[25] recently studied the so-called pulmonocoronary vagal reflexes in the dog and concluded that changes attributed to these reflexes are in reality a result of functional coronary insufficiency resulting from the low systemic blood pressure that is associated with the more severe types of acute pulmonary embolism. Villaret and his associates,[37] by means of studies on rabbits, noted that section of the vagus nerves increased by sevenfold the quantity of emboli necessary to produce death; section of the cervical sympathetic nerves reduced the quantity necessary by fourfold. Giving atropine and ephedrine delayed the occurrence of sudden death. De Takats, Beck, and Fenn[36] also considered vagal reflexes important in producing the low systemic blood pressure.

METHOD OF STUDY

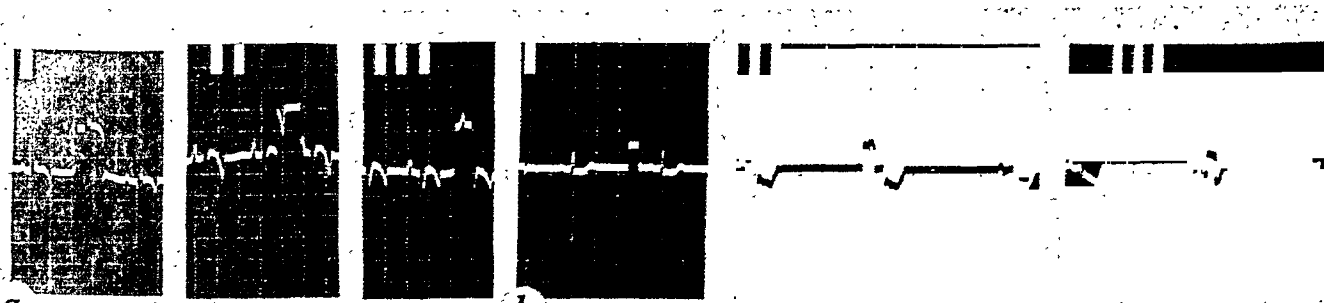
Acute pulmonary embolism was produced twenty-four times in ten dogs by rapid serial intravenous injections of a variable number of small particles; these particles were glass beads 3.0 mm. in diameter, rape seeds 1.5 to 2.0 mm. in diameter, or particles of sand 1.0 to 2.0 mm. in diameter. The glass beads were the most satisfactory. These particles were lined up in glass tubes of various lengths and physiologic solution of sodium chloride was used to wash them into the external jugular or femoral vein. Serial injections were continued until moderate tachypnea was produced; an increase of ten to fifty respirations per minute that persisted for at least two to three minutes was considered a good end point and was achieved in most cases. This increase in respiratory rate has been found to be a reliable indication of sublethal but large pulmonary emboli in dogs. Work along this line has been reported by several investigators.[6,7,26,29,30,36] With rare exceptions, this method produced embolism of a notable but nonfatal degree, although there was a wide variation in the number of particles necessary; for instance, from 150 to 350 rape seeds. The dogs weighed 9 to 15 kilograms and were apparently healthy mongrels. Both injections and electrocardiograms were made while the dogs were under anesthesia produced by the intravenous injection of 25 to 30 mg. of pentobarbital sodium per kilogram of body weight.

Electrocardiograms were made two or three times before the initial injection of embolic material, as well as between experiments and fifteen to 130 minutes after the completion of each experiment. The animal was placed on his back for the injections of the embolic material and on his right side for the electrocardiograms. A Sanborn Cardiette, with the sensitivity reduced one-half, was used throughout the experiment. The limb lead plates were applied with electrode jelly after the area was clipped and washed just as is done in man. Copper rivets, with heads about 1.0 cm. in diameter, were used as precordial electrodes; the skin was first prepared as for the limb leads. Five to nine precordial electrodes were used and they were held in place by means of perforations in a stiff rubber belt. They were spaced 1.25 inches (3.18 cm.) each way from the midline and were numbered I-IIII, IIII, IIII-I, IIII-II, II-III, IIII-III, IIII-IIII, IIII-IIIII and IIII-IIIIII) going from the right

side to the left side across the sternum; the sternum lead was II-III. The belt was applied so that Lead IIII-IIII was on the fifth rib. To check on the accuracy of the position of the belt, occasional control electrocardiograms were made with Lead IIII-IIII at the fourth, sixth, and seventh ribs, as well as at the fifth rib. Burnett[8] in a recent paper discussed changes in the precordial electrocardiograms due to the position of the exploring electrode. In our experiments, the limb lead electrocardiograms were the standard type, but the precordial electrocardiograms were the Goldberger[16] modification of the unipolar Wilson type.

RESULTS

In the limb leads there were significant changes in only five of the twenty-four electrocardiograms made after the injection of embolic material; the most marked changes were produced in a dog in which a fatal embolism was produced unintentionally. These changes consisted of elevation of RS-T_2 in four experiments and elevation of RS-T_3 in two; a negative T_2 and T_3 and a diphasic T_2 and T_3 (where the controls had quite consistently shown a positive T) appeared in one episode. In the animal in which fatal embolism was produced, there was a marked depression of RS-T_2; RS-T_3 and RS-T_1 were also somewhat depressed, and a previously negative T_1 became positive (Fig. 1). One



a b

Fig. 1.—Pulmonary embolism: *a*, before embolism; *b*, after embolism. In *b*, the RS-T_2 depression is marked; a lesser degree of RS-T depression is present in Leads I and III. T_1 has become positive. The control electrocardiogram, *a*, shows the extreme inversion of the T waves in all leads that may be encountered in apparently normal dogs. (In *a*, 1.0 cm. = 1.0 mv., and in *b*, 0.5 cm. = 1.0 mv.; in all subsequent figures, the sensitivity is reduced so that 0.5 cm. = 1.0 mv., as can be seen in the occasional standardizations.)

animal exhibited a slight shift of the electric axis to the right. The precordial leads in these experiments showed very minor changes. Decreased positivity of the T wave in leads over the right precordium appeared in the electrocardiogram of one animal and slight elevation of RS-T in leads over the left precordium appeared in two other animals. These changes were of doubtful significance.

These changes are certainly quite minimal; perhaps, as previously mentioned, this is due to the fact that a greater degree of pulmonary obstruction is necessary to cause dynamic changes in the dog than is apparently necessary in man. Whether pulmonary arterial spasm is an important factor in either the

dog or man is still a matter of conjecture. However, after reviewing the literature, we believe that these findings in dogs would not be in marked disagreement with the electrocardiographic changes found in instances of minor pulmonary embolism in man. One gets the impression that electrocardiographic changes are f equent in pulmonary embolism in man probably because (1) only cases in which these changes are present are usually reported and (2) usually only patients with the more severe clinical manifestations are investigated electrocardiographically. As noted previously, the precordial electrocardiogram was of little additional aid. However, this does not necessarily obtain in instances of more severe pulmonary embolism in the dog or in man. The frequent spontaneous reversal of the T waves in any of the standard leads makes it very difficult to evaluate the significance of the not infrequent reversal of the T wave in many of our dogs after the production of embolism. However, even the precordial lead T waves, although quite predictable in the dog, did not show any reversals. Currens and Barnes[12] quoted two different groups (de Takats, Beck, and Fenn[36] and Leriche, Fontaine, and Friedmann[22]) who found only minor obstruction of the pulmonary artery present in 20 and 30 per cent of patients dying of pulmonary embolism. This apparently does not obtain in the dog. Cullen and Rovenstine[10] reported three instances of sudden death of human beings when the hilus of the lung was ligated or cut with the electric cautery. Whether pulmonary arterial spasm occurs in man is conjectural; in the dog, it apparently is not a factor, for Gibbon and his associates[15] have demonstrated that at least 85 per cent of the pulmonary arterial flow must be blocked before death results. A better laboratory animal for the study of pulmonary embolism would be one in which smaller emboli could occasionally cause death and in which the normal electrocardiogram was of a more constant nature. Possibly the cat would fulfill the latter qualification[13]; in the dog, the use of direct ventricular leads might serve this same purpose.[39]

Even with larger and often fatal pulmonary emboli, the electrocardiographic changes in the dog are quite variable, judging from the findings of some of the authors mentioned.[9,30,32,40] To test this, we produced graded acute pulmonary arterial obstruction in seven dogs by using an adjustable snare around the pulmonary artery, somewhat as first used by Winans, Goode, and Ashworth.[40] We studied these animals with serial limb lead electrocardiograms until shortly before death. It was interesting to note that a marked degree of constriction was necessary to produce any changes in the electrocardiogram. Mann, Herrick, Essex, and Baldes[27] have demonstrated that constriction of the lumen of small arteries in animals may be surprisingly great without changing the rate of flow through the vessel as measured by the thermostromuhr. We did obtain significant electrocardiographic changes in all of these animals, but rather than being readily predictable, as indicated in the work of any one of a number of authors, the results were much like a composite of their work (Figs. 2 and 3). In general, RS-T deviation did occur, especially in Leads II and III, but this might be either elevation or depression, or indeed both might exist; elevation may be noted first or sometimes depression may be noted first. The T waves were not helpful, nor were there any S_1 or Q_3 waves where they were

not already present to the same degree in the control electrocardiogram. Since Q_3 is one of the changes observed in pulmonary embolism in man, it is of interest to note that Goldberger[17] expressed the opinion that unipolar limb leads are often necessary in the interpretation of standard limb lead Q waves, espe-

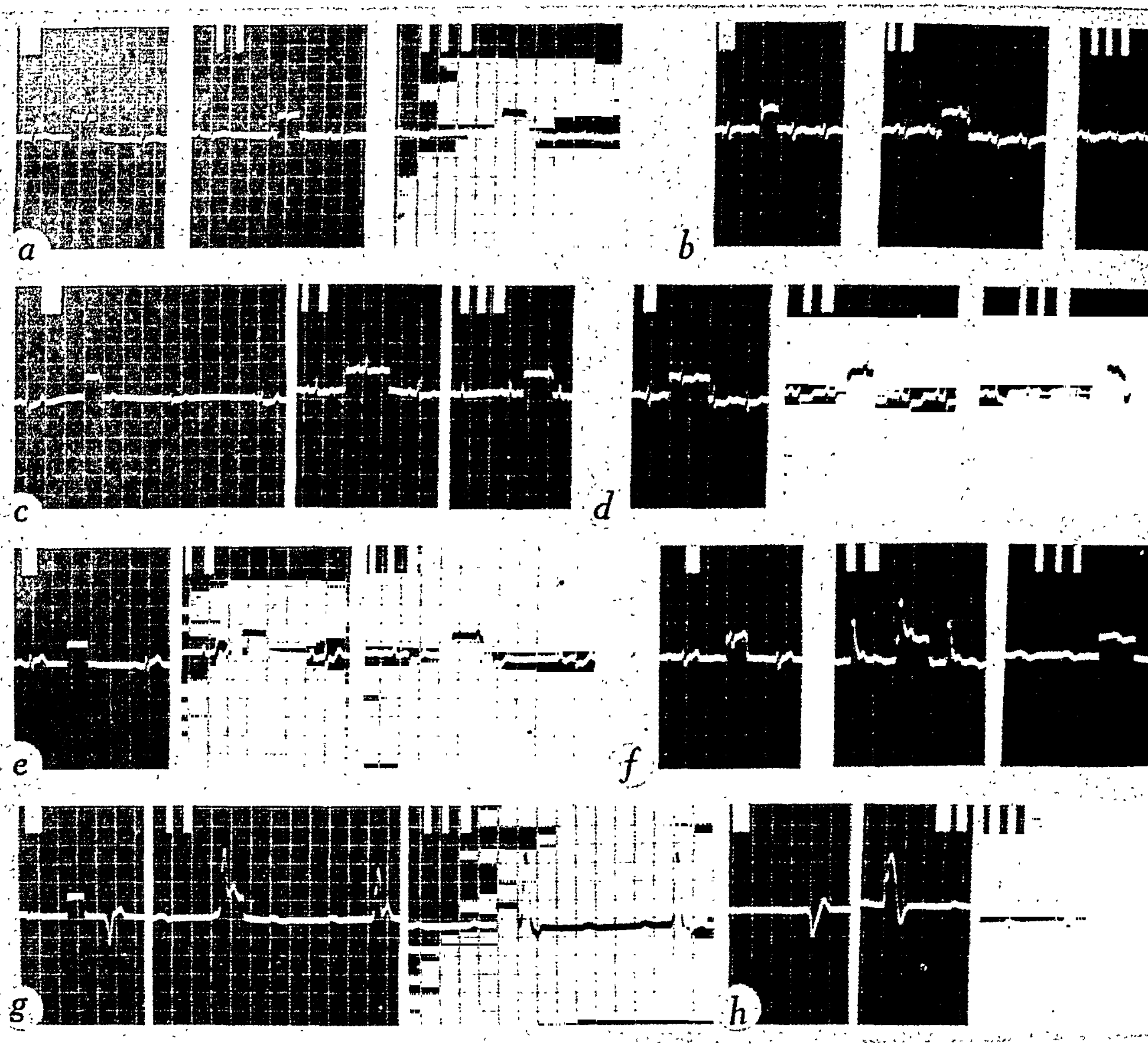


Fig. 2.—Pulmonary arterial constriction: *a*, before constriction; *b* through *h*, after gradually increased constrictions. The changes in order of appearance are: deepening of S_1; depression of $RS\text{-}T_1$; depression of $RS\text{-}T_2$ and $RS\text{-}T_3$, and a terminal disturbance of rhythm.

cially Q_3 waves. He noted that occasionally a large Q or QS in Lead III merely reflects a large R wave in the V_2 lead. Terminally, auriculoventricular dissociation, ventricular extrasystoles, auricular fibrillation, and other nonspecific changes in rhythm and conduction were often present in the electrocardiograms of our dogs. We also produced fatal pulmonary embolism in two dogs with an

overdosage of seeds; both animals showed definite and similar changes in the precordial electrocardiogram as well as in the limb leads. The changes in the limb leads were similar to those in the other instances of fatal pulmonary embolism just mentioned. The precordial electrocardiograms were made serially and showed depression of the RS-T segment in leads over the left precordium

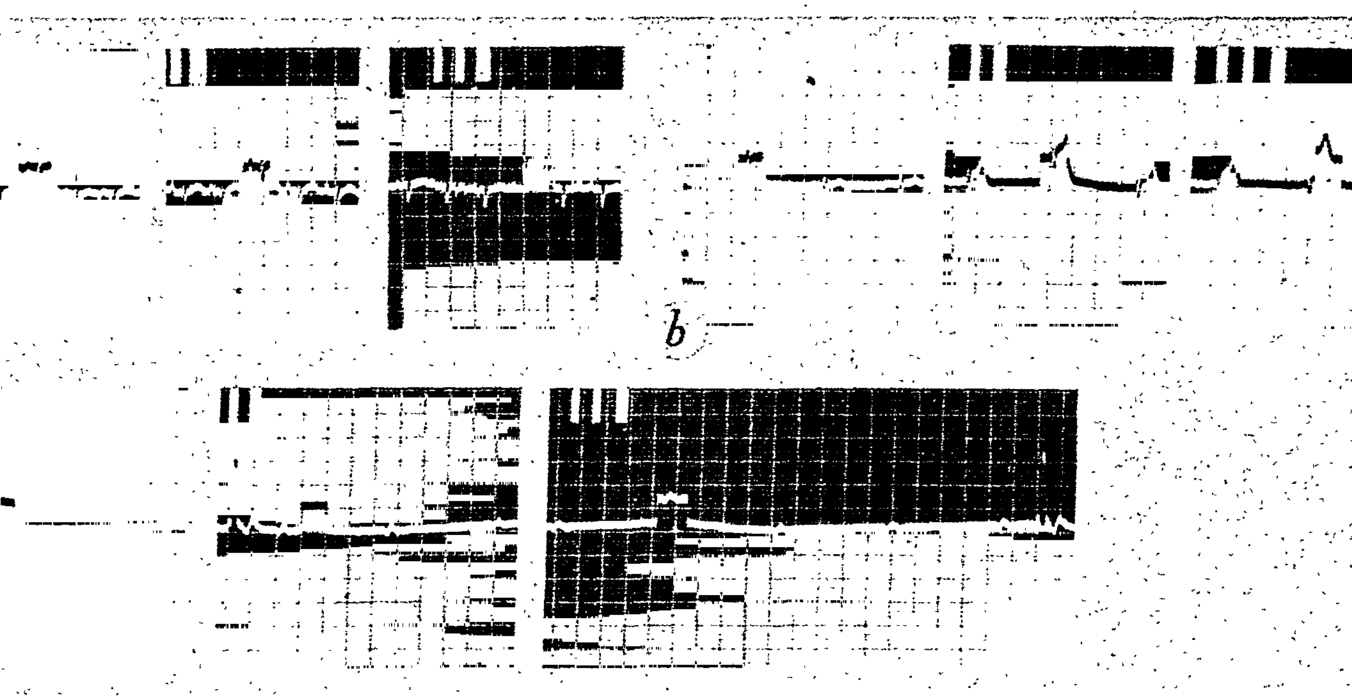


Fig. 3.—Pulmonary arterial constriction: *a*, before constriction; *b* and *c*, after gradually increased constriction. The changes consist of *b*, a well-marked elevation of RS-T_2 and RS-T_3, and *c*, a terminal disturbance of rhythm.

and elevation of the RS-T segment in leads taken over the right precordium. Inversion of the T wave in leads recorded over the right precordium, which is characteristic of the electrocardiogram of man, was not present (Fig. 4).

SUMMARY

It must be concluded that in the dog the electrocardiogram, including multiple unipolar precordial leads, is of limited value in the diagnosis of minor pulmonary embolism. In major pulmonary embolism in the dog, there are usually definite electrocardiographic changes, both in the limb leads and in the unipolar precordial leads. In the limb leads, the most constant change is deviation of the RS-T segment in Leads II and III; this may be either upward or downward. In man, the upward deviation of RS-T_2 has not been reported. In the precordial leads, there was depression of the RS-T segment in the left precordial leads and elevation of the RS-T segment in the right precordial leads. In man, elevation of the RS-T segment in the right precordial leads has rarely been reported.[34]

We did not attempt to evaluate the origin of these electrocardiographic changes; it has been suggested variously that they are due either to right ventricular strain or to myocardial anoxia.

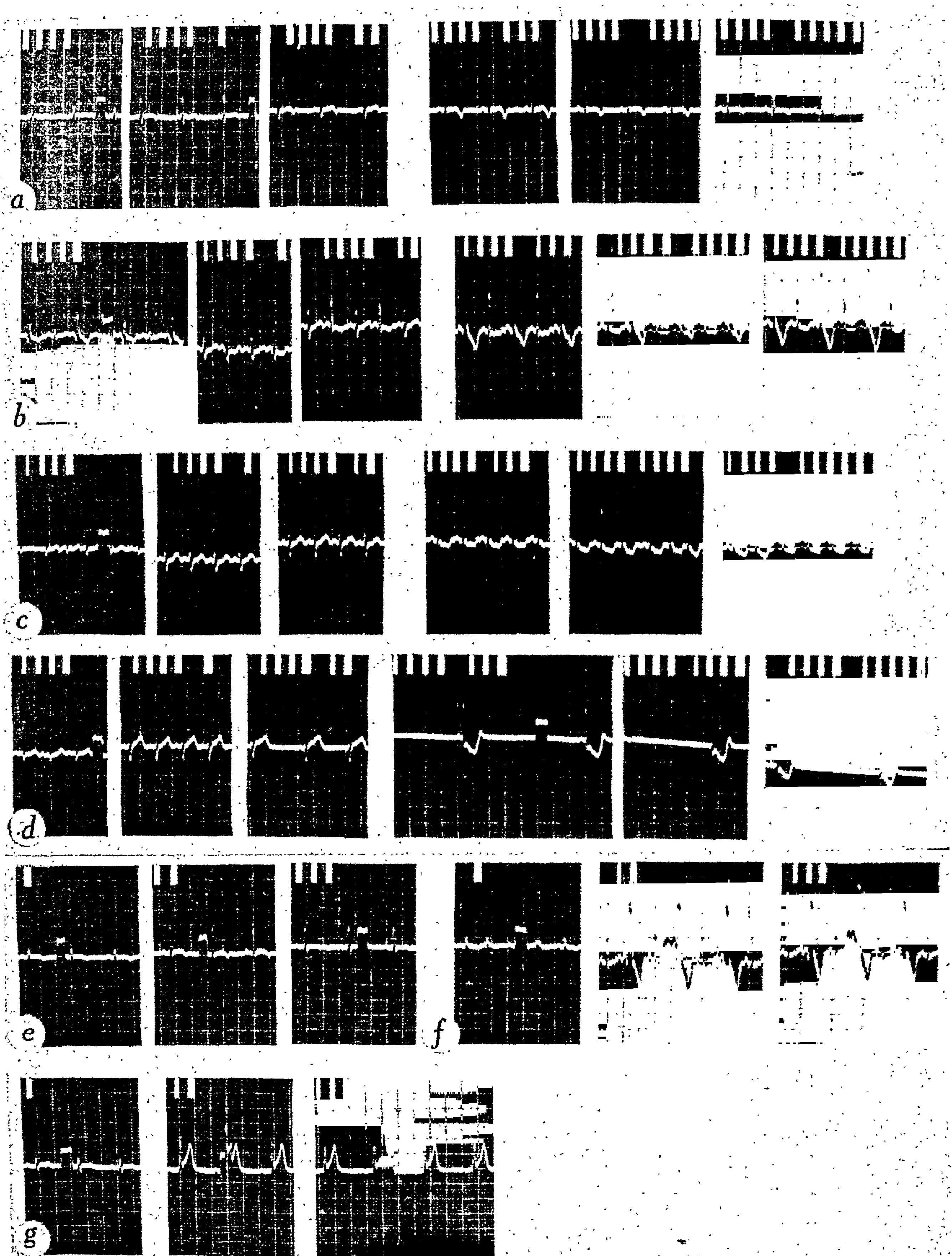


Fig. 4.—Pulmonary embolism: *a* through *d*, "unipolar" precordial leads; *a*, before embolism; *b*, *c*, and *d*, after gradually increased number of emboli; *e* through *g*, standard limb leads; *e*, before embolism; *f* and *g*, after gradually increased number of emboli.

In the precordial leads, aside from the disturbances of rhythm, the significant changes are RS-T depression in leads made over the left precordium (IIII-III through IIII-IIIII) and S-T elevation over the right precordium IIII through IIII-II). The limb leads show the development of an S wave in Lead I, elevated R-T junction in Leads II and III, and high amplitude of T_2 and T_3.

Previously in this paper attention has been called to the limitations of the electrocardiogram in the diagnosis of pulmonary embolism in man. But if a series of electrocardiograms are obtained in the first few days after pulmonary embolism occurs and if these are critically analyzed, valuable diagnostic aid can frequently be obtained. This study of the electrocardiograms of dogs in which pulmonary embolism has been induced experimentally would appear to support pessimism regarding the value of the electrocardiogram in the clinical diagnosis of pulmonary embolism. But it is by no means certain that these experiments in dogs duplicate the exact degree or exact mechanisms involved in pulmonary embolism in man. Furthermore, the electrocardiogram of the dog is more variable than is the electrocardiogram of man, so that electrocardiographic changes in the dog have to be of greater magnitude to have diagnostic significance.

While the results of these experiments should serve to warn us that the electrocardiogram often fails to aid in the diagnosis of minor pulmonary emboli in man, it should not be concluded from this study that the procedure possesses very limited clinical value.

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THE OXYGEN CONTENT OF CORONARY VENOUS BLOOD AS AFFECTED BY ANOXIA AND CYTOCHROME C*

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CYTOCHROME C has recently been advocated by Proger and Dekaneas[1,2] for the treatment of angina pectoris and coronary occlusion. The basis for its use is that under conditions of anoxia, it will enable the heart to remove some of the 75 to 80 per cent unused oxygen found in mixed venous blood in the right ventricle. Thus, the arteriovenous oxygen difference would widen (for example, from 4 volumes per cent to 6 volumes per cent), indicating increased uptake of oxygen from the blood by the anoxic tissues.[3] In patients demonstrating S-T segment depression in the electrocardiographic tracings during inhalation of 10 per cent oxygen mixtures, the injection of cytochrome C has been followed by the disappearance of the depression within two minutes.[1] This has been attributed to relief of myocardial anoxia through the action of cytochrome.

The theory upon which cytochrome is used presupposes several things, namely: (1) Under conditions of anoxia there are significant amounts of oxygen in coronary venous blood that could be utilized. (2) If such oxygen were present, cytochrome C could actually effect its removal.

Since a method was available for obtaining direct evidence on these questions,[4] it was deemed desirable to investigate the following factors pertaining to the oxygen content of coronary venous blood: (1) What are the normal values? (2) What is the effect of anoxia, per se, on these values? (3) What is the effect of the intravenous injection of cytochrome C?

METHODS

Two different methods have been utilized in this study:

1. *The Bubble Flowmeter Method.*—The techniques used here were the same as were outlined in a previous report.[4] In brief, dogs, averaging 17 kilograms in weight, were anesthetized with pentobarbital sodium intravenously. The animals' heparinized blood was then circuited from a cannulated right carotid artery, through the bubble flowmeter into a cannulated anterior descend-

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ing coronary artery. Coronary venous blood was obtained from a cannulated great cardiac vein and arterial blood from the femoral artery. The pneumothorax was evacuated and the animals allowed to breathe spontaneously.

2. *Catheterization Technique.*—In these experiments, the coronary sinus of the intact, lightly anesthetized dog was catheterized with fluoroscopic guidance, the method used being that reported by Goodale and associates[5] and utilized for the measurement of coronary blood flow[6] by the nitrous oxide method of Kety and Schmidt.[7,8] Coronary venous blood was thus obtained near the junction of the great cardiac vein and the coronary sinus. Arterial blood samples were collected from a femoral artery.

Blood samples were withdrawn into oiled syringes, the tips of which were filled with heparin. The arterial and venous samples were collected synchronously. The syringes were capped, immediately immersed in ice water, and placed in a refrigerator until the blood was analyzed for oxygen and carbon dioxide content by the method of Van Slyke and Neill.

The cytochrome C used in these experiments was obtained in sterile ampules,* each ampule containing 50 mg. of cytochrome C dissolved in 10 c.c. of normal saline. All injections were made intravenously in amounts varying from 3.8 to 12.5 mg. per kilogram of body weight.

RESULTS

The first consideration was the oxygen content of coronary venous blood obtained under our "normal" experimental conditions (that is, with the animal breathing room air or a gas mixture containing more than 21 per cent oxygen). Table I summarizes the data obtained in two groups of experiments in which: (a) the control animals were breathing 100 per cent oxygen (bubble flowmeter experiments) and (b) the control animals were breathing room air (catheterization experiments). The arterial and venous values are averages for the number of experiments indicated. In both groups the oxygen content of coronary venous blood was "normally" low. The coronary arteriovenous difference was about 13 volumes per cent, as compared with an average right ventricular arteriovenous difference of 4 volumes per cent.

TABLE I. "NORMAL" OXYGEN CONTENT OF CORONARY VENOUS BLOOD

	NO. EXPTS.	NO. OBSERV.	ARTERIAL O_2 (VOL. %)	VENOUS O_2 (VOL. %)	A-V O_2 DIFF. (VOL. %)
100% oxygen	10	19	19.0	5.7	13.3
Room air	10	17	16.4	2.9	13.5

*Kindly supplied by the Wyeth Institute of Applied Biochemistry, Philadelphia, Pa.

Table II summarizes our findings on the effect of anoxia on the coronary venous oxygen content. The control averages, with the animals breathing either room air (catheterization experiments) or 100 per cent oxygen (bubble flowmeter experiments), as well as the observations on the same animals with 10 per cent and 8 per cent oxygen, are presented for each group. These data indicate that with the low oxygen mixtures inhaled, the amount of oxygen remaining in the coronary venous blood was very small.

TABLE II. EFFECT OF ANOXIA ON CORONARY VENOUS OXYGEN CONTENT

	NO. EXPTS.	ARTERIAL O_2 (VOL. %)	VENOUS O_2 (VOL. %)	A-V O_2 DIFF. (VOL. %)
Room air (control)	4	17.5	5.4	12.1
10% oxygen		12.8	3.2	9.6
100% oxygen (control)	5	19.8	6.5	13.3
8% oxygen		9.5	2.0	7.5

Table III contains the average findings from a group of five experiments during which animals, made anoxic by the inhalation of 10 to 14 per cent oxygen mixtures, were given cytochrome C intravenously. The bubble flowmeter technique was used in all of these experiments. The control blood samples were withdrawn immediately before the injection of the cytochrome and the second pair collected an average of nine minutes after the injection.

TABLE III. EFFECT OF CYTOCHROME C ON THE CORONARY A-V OXYGEN DIFFERENCE

	CONTROL	AFTER CYTOCHROME C (AV. OF 9 MIN.)
Artery O_2 (vol. %)	13.7	12.2
Vein O_2 (vol. %)	4.2	3.5
A-V difference (vol. %)	9.5	8.7

No. experiments, 5.
Amount of cytochrome C injected, 3.8 to 7.8 mg/kg.

Table IV presents the oxygen data from three additional experiments where the catheterization technique was employed. The table indicates the chronological order in which the blood samples were removed and the oxygen and cytochrome C were administered.

TABLE IV. EFFECT OF CYTOCHROME C ON THE OXYGEN CONTENT OF CORONARY VENOUS BLOOD

EXP.	CONTROL	LOW O_2 MIXTURE INHALED (% O_2)	10 MIN.	15 MIN.	20 MIN.	30 MIN.	CYTOCHROME (MG./KG.)	15 MIN.	30 MIN.	45 MIN.
3. Artery (vol. %)	20.7	14		18.5		18.7	6.2	17.4		19.6
Vein (vol. %)	3.3			2.8		3.0		2.8		3.0
4. Artery (vol. %)	17.8	10	12.7		12.4		4.2	11 9	11.2	
Vein (vol. %)	8.6		2.0		1.8			1.8	1.9	
5. Artery (vol. %)	18.7	10	12.2		12 5		12.5	11.9	12.0	
Vein (vol. %)	7.3		2.7		2.7			2.3	2.0	

In only one of the eight animals did the arteriovenous oxygen difference increase (Table IV, Experiment 3). This occurred because the arterial oxygen content increased, apparently because of a change in the character of respirations which became full and deep following the injection of the cytochrome C. No such response was noted in the other dogs.

DISCUSSION

Data on the extremely low oxygen content of coronary venous blood have been presented before by Harrison, Friedman, and Resnik[9] and by Shipley and Gregg.[10] Our own work[4] has confirmed this and served to re-emphasize an important fact not sufficiently appreciated by many clinicians. Recent publications concerning the fortuitous catheterization of the coronary sinus of man[11,12] have led to the procurement of coronary venous blood samples whose oxygen content agrees well with that of samples obtained in the animal studies just referred to. It becomes difficult to see how appreciably larger quantities of oxygen can be removed by the heart when, under normal conditions, it is removing 75 to 80 per cent of the oxygen delivered to it.

Under conditions of anoxia, the oxygen supply to the myocardium is maintained primarily by an increase in the volume of coronary blood flow.[4] The shift in oxygen content of coronary venous blood is seldom more than 2 to 4 volumes per cent; consequently, a demand for more oxygen must be met by an increased coronary flow. This train of events is illustrated by the data contained in Table V. These observations were made in an experiment on the effect of anoxia on the coronary circulation and cardiac metabolism.[4] It is evident that under the conditions of anoxia, there are no significant quantities of oxygen left in the coronary venous blood that could be removed even if cytochrome C were to perform its expected action.

TABLE V. EFFECT OF ANOXIA ON THE CORONARY CIRCULATION
(Experiment 0-10*; Weight of Dog, 16.3 Kilograms)

O_2 MIXTURE INHALED (% OXYGEN)	100	21	16	12	8
Cor. Blood Flow (cc/100 Gm./min.)	54	82	106	176	264
Art. O_2 Content (vol. %)	19.5	15.7	11.2	7.9	4.0
Cor. Vein O_2 Content (vol. %)	3.5	2.4	1.8	1.1	0.6
Cardiac O_2 Consump. (cc/100 Gm./min.)	8.5	9.0	9.9	12.0	9.0

Coronary flow measured by the bubble flowmeter method.
*Pentobarbital sodium anesthesia.

As indicated by the data contained in Tables III and IV, we could detect no effect of cytochrome C on the removal of oxygen from coronary blood. The dosage of the drug used was equal to or greater than the amounts recommended by Proger and associates.[3] While it is true that the blood samples following cytochrome (Table III) were withdrawn after a comparatively short interval, one would have expected the changes to have occurred, if they were going to, on the basis of the reported improvement in two minutes following the injection of the drug in patients.

Since cytochrome C did not effect the removal of oxygen from coronary blood, the possibility remained that there might have been a stimulation to the coronary flow to increase the amount of oxygen delivered to the heart (coronary flow multiplied by the arterial oxygen content).[13] Coronary blood flow was measured in four of the experiments, summarized in Table III, and in none of the four did oxygen delivery or oxygen consumption increase.

In these experiments, therefore, we were unable to demonstrate that cytochrome C could increase the removal of oxygen from coronary blood. Nor were we able to find any evidence for an improvement in the oxygenation of the myocardium such as indicated by the report of Proger and Dekaneas.[3] These negative findings are in general agreement with other recently published reports[14,15] on the effect of cytochrome C.

SUMMARY

1. By means of the bubble flowmeter and the coronary sinus catheterization methods of investigating the coronary circulation of the dog, the "normal" values for the coronary venous oxygen content have been found to be 3 to 6 volumes per cent.

2. When 8 to 10 per cent oxygen mixtures were breathed, the oxygen content of coronary venous blood was reduced to 2 volumes per cent or less.

3. Increases in oxygen uptake by the heart were accomplished primarily by increases in the volume of coronary blood flow.

4. Cytochrome C, when injected intravenously in amounts varying from 3.8 to 12.5 mg. per kilogram of body weight, did not increase the coronary arteriovenous oxygen difference or the oxygen uptake of the heart.

We wish to express our appreciation to Dr. Carl F. Schmidt and Dr. Francis Wood for their interest and suggestions during this investigation.

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A PORTABLE ELECTRICAL MANOMETER SUITABLE FOR CONTINUOUS INDICATION OF PERIPHERAL VENOUS PRESSURES

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BECAUSE of the awkwardness and difficulty in handling a water manometer in hospital wards, there is need for a simpler means of measuring venous pressure. An instrument devised to fill this need is described herein.

MATERIAL AND METHODS

A resistance wire, strain gauge manometer coupled directly to a suitable galvanometer‡ as described by Lambert and Wood[1] for measuring and recording intra-arterial blood pressure was used.

The galvanometer, light source, and accessory optical and electrical systems were incorporated in a cabinet (Fig. 1), the outside dimensions of which are 17 by 9 by 10½ inches (43.2 by 22.9 by 26.7 cm.). The optical system consists of a light source,§ a condensing lens of 3.0 cm. focal length, the galvanometer mirror, two front surfaced mirrors measuring 1 by 4½ inches (2.5 by 11.4 cm.), mounted at opposite ends of the cabinet, and a ground glass screen incorporating a millimeter scale, 15 cm. in length. The optical distance from the galvanometer mirror to the screen is 1.06 meters. A hair line is projected onto the galvanometer mirror and brought to a focus on the ground glass screen by means of the condensing lens.¶

The electrical system exterior to the manometer consists of a stable voltage source,** the galvanometer, a small voltmeter,*** and two variable resistors. The circuit diagram is shown in Fig. 2. The batteries supply the voltage across the Wheatstone bridge circuit which is incorporated within the strain gauge manometer. One of the variable resistors serves to regulate the voltage across this Wheatstone bridge; hence, the sensitivity of the manometer. The voltage

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§Heiland Type A galvanometer. Manufactured by the Heiland Research Corporation, Denver, Colo.

115 volt, 15 watt bulb, code 15T 8/c. Manufactured by the General Electric Company, Cleveland, Ohio.

¶In more recent models of the instrument the image of the filament of a single filament bulb (10 volt, 3.5 amp., Code T 14, manufactured by the General Electric Company, Cleveland, Ohio) has been focused onto the ground glass screen in place of the hair line. This light source is powered from a transformer (10 volt, 3.5 amp., No. AX 1162, manufactured especially for this instrument by the Audio Development Company, Minneapolis, Minn.) activated by 115 volts A.C.

**Two six-volt, four-cell Eveready lantern batteries.

***Zero to 1 milliammeter with an internal resistance of 50 ohms.

across the bridge is indicated on the voltmeter which is mounted on the front panel of the cabinet. The second resistor is used as an accessory calibrating device to check the response of the instrument to a given change in resistance in the bridge circuit. The wash bottle* for the manometer system is also contained within the cabinet. Pressure in the wash bottle can be regulated to any desired level by means of a hand bulb and a Tycos manometer which are mounted on the front panel of the cabinet (Fig. 1).

The strain gauges are attached to the top of the cabinet by means of brackets. A strain gauge manometer† with a pressure range of ±20 mm. of mercury has been found suitable for the measurement of peripheral venous pressure. When used with 10 volts across the bridge circuit, this manometer produces a galvanometer deflection of 7 mm. per centimeter of water and is linear throughout its pressure range. The sensitivity of the manometer can be reduced to any degree by reduction of the input voltage. The manometer is equipped with a lucite adapter, as described by Lambert and Wood, so that the detection and removal of air bubbles from the system is greatly facilitated. The manometer is connected to a 19 or 20 gauge hypodermic needle by means of an adapter and an 86 cm. length of 1.6 mm. I.D. polythene tubing. The volume displacement of the entire system per 10 mm. of mercury pressure is 22 cubic millimeters. The manometer system is overdamped. The instrument requires 0.75 second to register 95 per cent of the full response to an instantaneous pressure change.

The instrument weighs 21 pounds (9.5 kilograms) and is sufficiently rugged so that it can be transported by carrying. A handle is mounted on the top of the cabinet to facilitate handling of the instrument.

Venous pressure determinations with this instrument have been carried out as follows:

The patient is kept at rest in the supine position for at least fifteen minutes. If he is not lying on a rigid-topped couch, a board which is at least as long as the width of the bed and about 8 inches (20.3 cm.) wide is placed under the scapulae. The arm is abducted to form an angle of about 40° and is placed below the mid-thoracic level. The strain gauge is placed at approximately the same height as the antecubital space and a reading is taken with the needle lying on the skin of the antecubital space just above the vein. A 19 or 20 gauge needle is inserted into the antecubital vein and the strain gauge adapter attached when it is certain that all air bubbles have been expressed from the system. If the venous pressure is elevated to a degree that produces an off-scale deflection of the instrument, the voltage is reduced so as to bring the hair line onto the scale. The voltage is checked during the test to see that it is maintained at a constant value. The manometer system is flushed with heparinized saline solution (10 mg. sodium heparin is added to each 500 c.c. of 0.9 per cent saline solution) for a second or two before readings are made. When three similar consecutive readings, taken at intervals of approximately thirty seconds, are obtained, they are taken as the venous pressure. The venous pressure usually stabilizes to this degree in from

*A brass adapter top was devised so that an ordinary 500 c.c. Baxter bottle of sterile 0.9 per cent saline solution could be utilized.

†Model No. P5-0.4D-350, Statham Laboratories, Los Angeles, Calif.

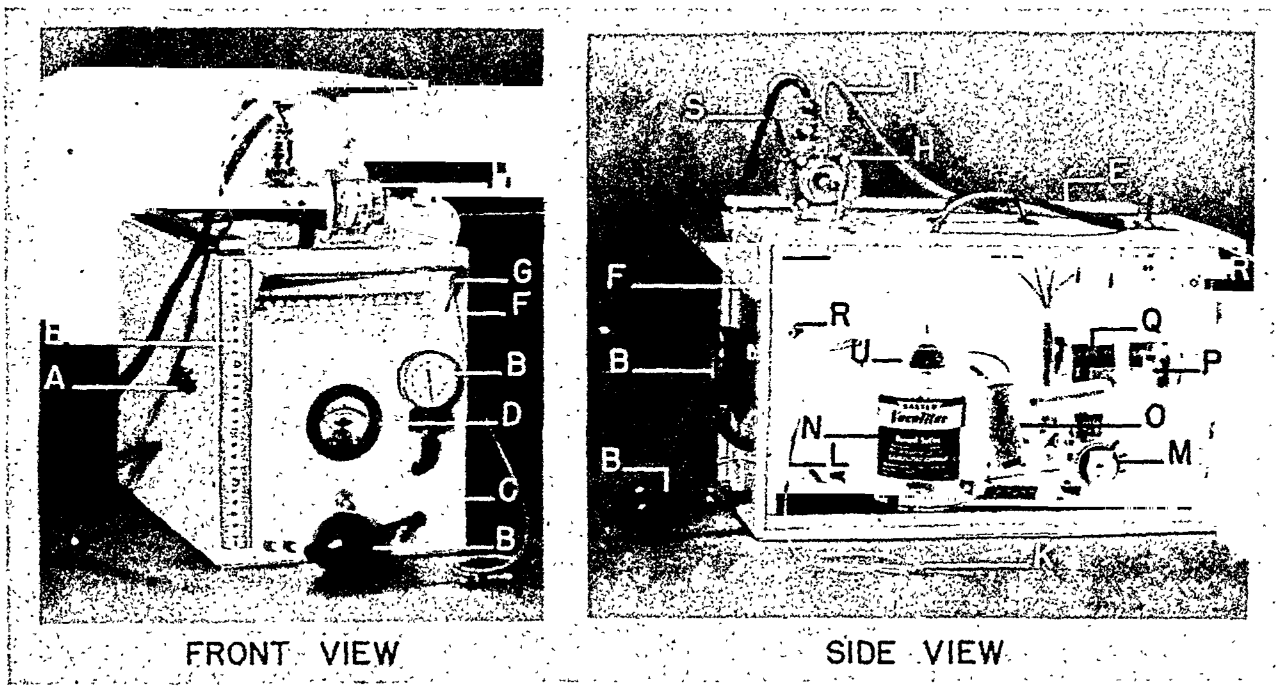

Fig. 1.—Portable strain gauge manometer. *A*, Calibration switch; *B*, pressure bulb and Tycos manometer for wash bottle; *C*, battery switch; *D*, voltmeter; *E*, calibration scale in centimeters; *F*, ground glass screen; *G*, shade; *H*, strain gauge manometer; *K*, glass adapter and needle; *L*, polythene tubing; *M*, voltage control; *N*, wash bottle; *O*, light source; *P*, galvanometer; *Q*, batteries; *R*, mirrors; *S*, lead wires; *T*, wash tubing; *U*, adapter top for wash bottle.

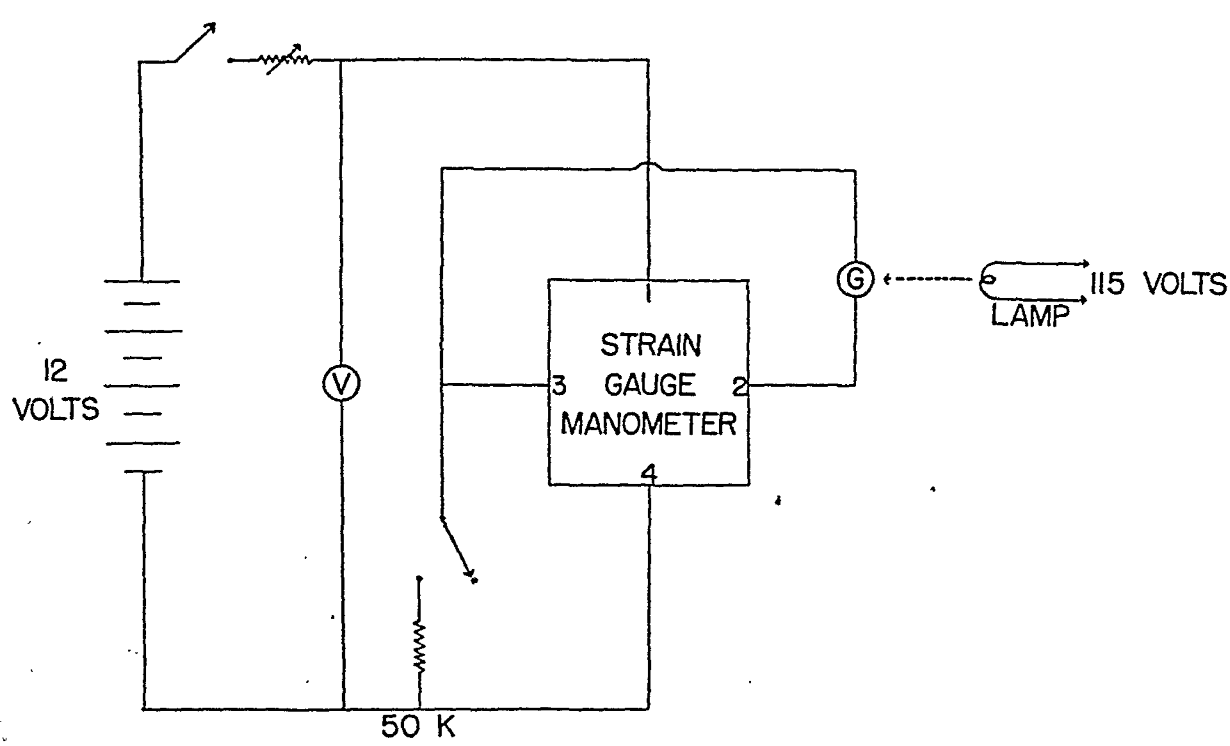

Fig. 2.—Circuit diagram. Portable strain gauge manometer.

five to fifteen minutes after the venipuncture has been completed. When stable readings are obtained, the needle is removed from the vein. The needle and a small amount of fluid are removed from the glass adapter so that the resulting meniscus lies near the middle of the barrel of the adapter. The adapter is then placed horizontally on the top of the board which was inserted under the patient's back and a reading is taken. The adapter is placed at the third intercostal space just to the right of the sternum and a second reading is taken. These two readings serve to measure the anteroposterior diameter of the patient's thorax at the level of the third intercostal space and provide a basis for determining the zero point to be selected for the venous pressure readings.

Calibration is simple and speedy. The meniscus in the adapter is leveled with different points on a vertical centimeter scale mounted on the front panel of the cabinet (Fig. 1). Readings are taken at four or five equidistant points on this scale selected so that the range of pressures encountered in the test is covered by these calibration readings. The galvanometer readings are plotted against the scale readings (centimeters of water). This calibration curve has uniformly been found to be linear. The galvanometer readings obtained during the test are readily converted to pressure (centimeters of water) by use of this calibration curve. The zero or reference point can be taken at (1) the midpoint of the anteroposterior diameter of the thorax at the level of the third intercostal space or (2) 10 cm. above the skin of the back or at any other point, covered by the calibration, which may be selected.

The venous pressure readings obtained by means of the strain gauge manometer were compared with those obtained by the use of the water manometer in the following manner: A water manometer was fixed to a wooden couch in such a fashion that the manometer was perpendicular to the couch top, with the zero of the scale at couch top level. The patient reclined on the couch top for about fifteen minutes. When the patient was in the supine position the anteroposterior diameter of his thorax was measured at the level of the third intercostal space by the use of calipers, as well as by the placing of the adapter of the strain gauge at the third right intercostal space just next to the sternum and on the couch top both before and after the test. An ordinary 20 gauge needle was inserted into the antecubital vein and attached to a three-way stopcock. The adapters of the water manometer and strain gauge manometer were then attached to the stopcock and the pressures recorded alternately after stabilization of the venous pressure.

The capillarity of the water manometer was determined as 5.0 mm. of saline solution; consequently, this figure was subtracted from the water manometer readings. Capillarity likewise becomes a factor during the calibration of the strain gauge manometer. The capillary action of the glass adapter used in these experiments supported a fluid column of 12 mm. of saline solution. This figure was subtracted from the calibration curve for the instrument. In the study of ten normal subjects between the ages of 20 and 35 years, the differences between the venous pressures as measured by the water manometer and the strain gauge manometer ranged from -0.5 cm. to $+0.9$ cm. of saline solution (Table I). On the average, the strain gauge readings were 0.08 cm. of saline solution above the

TABLE I. COMPARISON OF THE VENOUS PRESSURE IN NORMAL SUBJECTS AS DETERMINED BY A WATER MANOMETER AND A STRAIN GAUGE MANOMETER

SUBJECT	VENOUS PRESSURE MEASURED BY WATER MANOMETER (CM. OF SALINE SOLUTION)	VENOUS PRESSURE MEASURED BY STRAIN GAUGE MANOMETER (CM. OF SALINE SOLUTION)	DIFFERENCE (CM. OF SALINE SOLUTION)
1	11.8	11.9	0.1
2	9.9	10.2	0.3
3	9.5	9.9	0.4
4	10.6	11.5	0.9
5	12.6	12.7	0.1
6	13.6	13.2	−0.4
7	13.2	13.1	−0.1
8	10.2	9.9	−0.3
9	9.8	10.1	0.3
10	10.6	10.1	−0.5
Average values	11.2 ± 0.5*	11.3 ± 0.4*	0.08

*The figure following the ± sign is the standard error of the mean.

readings obtained by the water manometer. This difference, however, was not considered statistically significant since the p value was greater than 0.5 (Table I).

COMMENT

The literature contains many reference points for the site of the right auricle with reference to various parts of the body in the supine position. Bloomfield and his associates,[2] after taking measurements from lateral roentgenograms, felt that 5.0 cm. below the angle of Louis was the point from which to calculate venous pressure as well as right heart pressure. Winsor and Burch[3] have described a phlebostatic axis and a phlebostatic level for measurement of venous pressures. Lyons, Kennedy, and Burwell[4] reviewed the literature and listed several tables with different reference points and the normal values for the venous pressure as determined from these points by the various authors. They found that the great majority of the range of normal venous pressures falls between 5.0 cm. and 15 cm. of saline solution. They measured the height of the right auricle from the skin of the back in frozen sections of cadavers as well as by means of fluoroscopy and felt that 10 cm. from the skin of the back was an accurate point from which to measure venous pressure in an adult. However, difficulty has been encountered in use of such a reference point for female patients since the anteroposterior diameter of the thorax in some cases is approximately 10 cm. or less.

At this laboratory it was decided to use the midpoint of the anteroposterior diameter of the thorax measured at the level of the third right intercostal space since this is about the level of the middle of the right auricle as given by Cunningham.[5] In ten normal subjects the range of venous pressure was found to fall within 5.0 to 15 cm. of saline solution measured both by water manometer and

strain gauge with the midpoint of the anteroposterior diameter of the thorax at the level of the third intercostal space as the reference point.

When the deflection of the galvanometer was read, it was noted that rhythmic fluctuations of the hair line ranged from 2.0 to 5.0 millimeters. These fluctuations are caused partly by respiration and partly by transmission of the venous pulse wave. The mean value of these pressure fluctuations has been taken as the venous pressure.

This instrument* is simple to operate and a technician was easily taught to determine venous pressures without assistance in a few days. Since the instrument weighs 21 pounds, it can be carried for short distances and rolled on a cart if greater distances must be covered by the technician. The instrument we use is transported to two different hospitals, as well as to the cardiovascular laboratory, in its daily use. The accuracy of this type of manometer already has been discussed by Lambert and Wood, and the comparison of measurements made by the water manometer and strain gauge demonstrates further the degree of exactness of the determinations.

SUMMARY

A portable electrical manometer suitable for continuous indication of peripheral venous pressure has been described. Resting venous pressure in the arm in the supine position was determined in ten normal subjects and found to be 11.3 cm. of saline, with a range of 9.9 to 13.2 centimeters.

ADDENDUM

By use of a strain gauge the range of which is ±200 mm. of mercury (Model P 6-4D-250), this instrument has been used for continuous measurement of pressure during atrial catheterization. Because the instrument can be read in the dark, pressures can be determined as the catheter is being advanced under the fluoroscope, thus greatly facilitating the procedure of determining the exact moment of entry or withdrawal from the right ventricle or pulmonary artery.

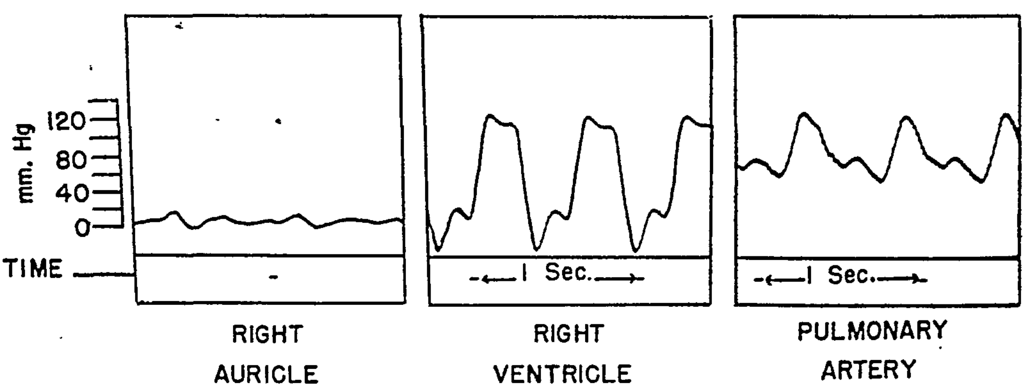

Fig. 3.—Photokymographic tracings of pressures during atrial catheterization. The patient was an 11-year-old white boy with patent ductus arteriosus complicated by pulmonary hypertension.

*A modification of this instrument can be obtained from the Waters Conley Company, Rochester, Minn.

Photographic recording of the pressures has been made simultaneously with the visual readings (Fig. 3) by connecting a recording galvanometer* in series with the galvanometer of the instrument. The frequency characteristics of the combined manometer-catheter system precludes the use of the instrument in its present form for accurate studies of ventricular pressure pulse contours.

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*A Heiland Type A galvanometer incorporated in a Heiland Type A 401 R-6 oscillograph. Manufactured by the Heiland Research Corporation, Denver, Colo.

CAN THE LONGITUDINAL ANATOMICAL AXIS OF THE VENTRICLES BE ESTIMATED FROM THE ELECTROCARDIOGRAM?

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IN AN earlier paper[1] it was stated that it is possible to estimate with reasonable accuracy the longitudinal anatomical axis of the human ventricles ($\hat{H}$) from the QRS complex of the electrocardiogram. By use of an adaptation of the method first proposed by Gardberg and Ashman,[2] estimates of the axis, $\hat{H}$, were made for thirty-six cases in Master's book.[3] In thirty-four of thirty-six cases, the axis measured on the x-ray plate and the axis estimated from the electrocardiogram differed by not over 7 degrees. In one case the difference was 8°, and in another it was 12 degrees. It was admitted that the estimate may unconsciously have been influenced by knowledge of the teleroentgenogram. Further evidence was adduced to demonstrate that estimates from the electrocardiogram are fairly accurate, but the evidence was indirect. Since we proposed making use of the method in a study of the electrocardiographic changes in thyrotoxicosis, a direct test of the question seemed to be desirable.

METHOD

The direction of H was determined by orthodiagram in a series of fifty normal persons, most of whom were on the staff of or employed by the Cincinnati General Hospital. The standard limb-lead electrocardiogram was also taken on each of these individuals, the body position being the same as that during the fluoroscopic examination. Children were excluded from the series. The electrocardiograms were then sent to the third author, with no additional information. The latter excluded two of these fifty electrocardiograms because of the presence of a delay in right bundle branch conduction. (This is seen in a small percentage of persons who present no clinical evidence of heart disease.) Two other records were excluded because the technique was untrustworthy. A fifth electrocardiogram was rejected because it was clearly abnormal, the P-R intervals being long and variable and the QRS complexes low and of unusual configuration. Thus, the electrocardiograms of forty-five subjects remained. In each of these subjects, $\hat{H}$, the longitudinal ventricular axis, was estimated according to the method previously described.[4,5] In most instances, the estimate was based on the charts shown in those papers. In only a few cases was the QRS loop of the vector-

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cardiogram constructed as an aid in finding the $\hat{H}$ direction. In addition, in each case the mean manifest QRS axis ($\hat{A}_{QRS}$) and its magnitude (A_{QRS}), and also $\hat{G}$ (the mean manifest QRS-T axis or ventricular gradient of Wilson) and its magnitude (G), were estimated.[6]

RESULTS

Table I shows the results of our study. In the first column is the subject's number. In the second column is the direction of $\hat{H}$ as measured by the orthodiagram. In six instances, two separate estimates are shown for the same subject. In these the $\hat{H}$ axis was re-estimated; the second estimate is given below the first. In the third column the electrocardiographic estimate of $\hat{H}$ is given; and in the fourth column is shown the difference in degrees between the estimates by the two methods. It will be observed that in thirty-seven of the forty-five subjects the angle between the two estimates of $\hat{H}$ is less than 10°; in forty-three cases it is less than 12°; in one case it was 14°; and in one case it was 15 degrees.

When the estimates of $\hat{H}$ based on the electrocardiogram reached Cincinnati, the six subjects in whom the difference between the two estimates exceeded 10° were re-examined. As the table shows, in four of these six subjects, remeasurement lessened the discrepancy between the findings by the two methods. In two subjects the second orthodiagram confirmed the first. (Remeasurements are shown in parentheses in the table.)

DISCUSSION

The first question which must be asked is: Are the apparent agreements between the $\hat{H}$ axes, estimated by the two methods, significant? Is it not possible that if one were to guess $\hat{H}$ in all instances to be +40° (which is about the average direction), the agreement between this $\hat{H}$ and the estimate by orthodiagram would be as good as the agreement shown by the table?

An answer to this question can be obtained only by statistical methods. The first step is to assume that the $\hat{H}$ axis given by the orthodiagram is the correct one. Then, for each electrocardiographic estimate of $\hat{H}$ there is either no error (the two estimates being in agreement), or else the electrical estimate is in error because the indicated direction of $\hat{H}$ is to the right or to the left of the orthodiagrammatic finding. We can plot these "errors" and calculate their standard deviation from the mean. On the average, the $\hat{H}$ axis is electrically estimated to point $1.94 \pm 0.57°$ to the right of its "true" (orthodiagram) direction. The standard deviation of the discrepancies between the two estimates is 5.66 ± 0.41 degrees.* This figure suggests that in a comparable series of persons it should be possible to estimate $\hat{H}$ from the electrocardiogram alone with an error of less than 15° in ninety-nine out of one hundred cases. It should be noted that these calculations are based on the original orthodiagrammatic

*If the standard deviation is calculated, using the $\hat{H}$ found on re-examination, it falls to 4.95 ± 0.35 degrees.

measurements. No correlation was found between the body build and extent of error.

But it may be true that if we guessed all axes to be +40°, as we have suggested, the errors would be no greater. When this is done, the standard devia-

TABLE I. COMPARISON OF THE ELECTROCARDIOGRAPHIC AND ORTHODIAGRAMMATIC ESTIMATES OF $\hat{H}$

SUBJECTS' NUMBER	$\hat{H}$ FROM ORTHODIAGRAM (DEGREES)	$\hat{H}$ FROM ECG (DEGREES)	DIFFERENCE, ECG ESTIMATE TO RIGHT OR LEFT OF ORTHODIAGRAMMATIC (DEGREES)
3	47	48	1 R
4	50	54	4 R
5	47	52	3 R
6	43	54	11 R
	(43)		
7	29	25	4 L
8	48	42	6 L
9	52	50	2 L
10	37	39	2 R
12	52	52	0
14	33	41	8 R
15	43	40	3 L
16	32	35	3 R
17	44	54	10 R
18	45	60	15 R
	(51)		(9 R)
19	49	60	11 R
	(49)		
20	47	50	3 R
21	34	45	11 R
	(36)		(9 R)
22	51	42	9 L
23	50	45	5 R
24	52	45	7 L
25	58	47	11 L
	(45)		(2 R)
26	48	53	5 R
27	42	44	2 R
28	35	35	0
29	37	38	1 R
30	47	48	1 R
31	45	41	4 L
32	48	55	7 R
33	35	42	7 R
34	39	53	14 R
	(46)		(7 R)
35	48	43	5 L
36	30	26	4 L
37	35	40	5 R
38	28	24	4 L
39	50	55	5 R
40	44	40	4 L
41	43	42	1 L
42	35	34	1 L
43	51	50	1 L
44	39	44	5 R
45	38	42	4 R
46	34	37	3 R
48	24	31	7 R
49	39	49	10 R
50	27	29	2 R

tion of the "errors" rises to 8.10 ± 0.58 degrees. The difference between this figure and 5.66 ± 0.41° is 2.44 ± 0.70 degrees. Since the difference is three and one-half times its probable error, we may conclude that the electrocardiographic estimate is considerably more reliable than an estimate of all axes as +40°.

A fairer test of the relative accuracy of the method, however, seems to be to compare the electrocardiographic estimate of $\hat{H}$ of each subject with the orthodiagrammatic estimate of the next subject on the list. When this is done, the standard deviation of the errors rises to 12.30 ± 0.88 degrees. The difference between this figure and the standard deviation of 5.66 ± 0.41 is 6.64 ± 0.97 degrees. Since that difference is nearly seven times its probable error, it is highly significant and demonstrates that $\hat{H}$ can be estimated with fair accuracy from the electrocardiogram.

Thus far in the discussion it has been assumed that the estimate of $\hat{H}$ from the orthodiagram is correct. It is our opinion that the orthodiagrammatic estimate may be as much in error as the electrocardiographic estimate. Thus, if the electrocardiogram errs in one direction and the fluoroscope in the other, the discrepancy may be large, and misleading. Some evidence tends to support this belief: (1) Careful remeasurement of $\hat{H}$ in the six subjects showing the greatest discrepancy reduced the "error" in four cases, though the remeasurements are not included in the statistical analysis. (2) In the series from Master's book, the $\hat{H}$ axis shown by the teleroentgenogram had been measured and remeasured until it was felt that the estimates were as accurate as possible. In only one of the thirty-six subjects did the "error" exceed 8°, and in that particular case it is likely that the electrocardiogram and roentgenogram were not taken with the patient in the same position. (3) Further evidence is obtained from a study of $\hat{G}$. Ashman has reported that the standard deviation of the deviations of $\hat{G}$ from their estimated average directions in a series of 164 adults was 7.38 ± 0.28 degrees. In our present series of cases, the standard deviation of $\hat{G}$, when the electrocardiographic estimate of $\hat{H}$ is used, is 7.66 ± 0.55 degrees. This latter is not significantly different from the previously reported figure. When the study of the gradient deviation is based upon the orthodiagrammatic measurements in the present series of cases, the standard deviation rises to 8.61 ± 0.62 degrees. Although the two figures are not significantly different in a statistical sense, they add some slight support to the view that the electrocardiographic estimate of H may have been more accurate than the fluoroscopic estimate in this study.

It may be noted in conclusion that the method used in estimating $\hat{H}$ from the electrocardiogram may be open to further refinement. It is, therefore, possible that greater accuracy may ultimately be attained.

SUMMARY

The direction of the longitudinal anatomical axis of the ventricles was estimated from the orthodiagram in each of forty-five normal persons. Quite independently, the same estimate was made from the QRS complex of the electrocardiogram, taken in the same recumbent body position. The two series of

estimates were then compared. It is concluded that the form of the QRS complex correctly indicates the direction of the anatomical axis in a large majority of normal persons.

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EVALUATION OF THE PRECORDIAL LEADS OF THE ELECTROCARDIOGRAM IN OBESITY

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IT IS well known that in obesity and other conditions associated with a transverse position of the heart the standard leads in the electrocardiogram frequently present a characteristic pattern, namely, left axis deviation and inversion of the T and P waves in Lead III[1,2]; frequently there is a large Q wave in Lead III and occasionally the T wave is low in Lead II. These changes may be difficult to differentiate from those produced by myocardial disease, particularly previous coronary occlusion with posterior infarction. For a number of years we[2] have also occasionally observed T-wave inversion in Lead CF_4 in normal obese persons, a finding usually considered abnormal.[3-6] Since no systematic study of the precordial electrocardiogram in obesity had been reported, an investigation was undertaken to determine whether the chest leads in obese subjects differed from those in normal persons.

The study was considered to be pertinent to two current and related controversial subjects; namely, the limits of the normal T wave in the six official chest positions[7] and the relative value of the location of the indifferent electrode, whether the right arm, left arm, left leg, or the common terminal of Wilson[8] (CR, CL, CF, or V leads). In the past, CF leads have usually been used routinely and the majority of reports in the literature, based on the use of these leads alone, state that the T wave is normally upright in Positions 2 to 6 except that it is diphasic in Lead CF_2 in approximately 1 per cent of cases.[3-6] Yet T-wave inversion has occasionally been observed in Lead CF_4 in presumably normal persons[9] and in those with autonomic imbalance or neurocirculatory asthenia.[2,10] Similar inconsistencies were encountered in CL and CR leads. Comparison of the CF, CL, and CR leads demonstrated differences between them and certain advantages were pointed out for each.[3,11,12] This resulted in considerable complexity and uncertainty in the use of chest leads. In 1934, Wilson and his coworkers[8] introduced a common terminal (unipolar, V leads), thus obviating the distorting influence of the extremity potentials on the chest leads. It is well established that the CR, CL, and CF leads, which are supposed to register the electrical activity immediately beneath the precordial electrode, are affected by the potentials from the right arm, left arm, and left foot, respectively. In other words, the "indifferent" extremity electrodes are not completely neutral. A positive extremity potential has a "negative" influence on the precordial electro-

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Table I. Electrocardiographic Findings in Thirty-four Obese Women

PATIENT	AGE	HT.	WT.	AXIS	STANDARD LEADS	T WAVE IN CHEST LEADS
1 (L. S.)	44	5'6"	208	LAD	Q_3, T_3 inverted	CF_1 inverted
2 (M. H.)	41	5'5"	396	LAD	Q_3, T_3 inverted	CF_1 iseoelectric
3 (M. M.)	36	5'6"	187	LAD	T_3 inverted	$CF_{1,2}$ inverted
4 (H. W.)	52	5'2"	195	LAD	Q_3, T_3 inverted	
5 (S. J.)	43	5'7"	230	LAD		Q present in $CF_{1,2}$; $CF_{1,4}$ inverted, varies with respiration; CR normal
6 (R. K.)	42	5'2"	172	LAD		CF_1 inverted
7 (M. F.)	39	5'6"	187	LAD		CF_1 inverted
8 (A. K.)	40	5'6"	215	LAD	Q_3, P_3, T_3 inverted	CF_1 inverted
9 (H. J.)	37	5'8"	216	LAD		CF_1 inverted
10 (B. W.)	51	5'2"	229	LAD		$CF_{1,2}$ inverted; CF_2 inverted, varies with respiration; CR normal
11 (R. A.)	47	5'1"	186	None		CF_1 inverted
12 (R. M.)	36	4'7"	158	LAD		CF_1 inverted
13 (S. A.)	42	5'2"	260	None	T_1 low	CF_{1-6} inverted CR_{4-6} diphasic
14 (J. L.)	21	5'3"	221	None		CF_1 inverted
15 (C. M.)	52	5'7"	244	LAD	Q_3, P_3, T_3	CF_1 inverted
16 (M. B.)	64	5'4"	191	LAD		CF_1 inverted
17 (E. S.)	50	5'1"	187	None		CF_{1-5} inverted, CF_6 isoelectric; CR normal; after weight reduction, CF normal
18 (F. H.)	42	5'2"	160	LAD		$CF_{1,2}$ inverted; CR normal
19 (E. K.)	50	5'7"	206	LAD		
20 (R. K.)	28	5'6"	182	LAD		CF_1 inverted
21 (B. Z.)	53	5'8"	175	LAD		CF_1 inverted
22 (D. S.)	46	5'1"	156	LAD	Q_3, T_3 inverted	$CF_{1,2}$ inverted
23 (N. R.)	50	5'6"	215	LAD		CF_1 inverted; CF_6 varies with respiration
24 (G. S.)	40	5'2"	194	LAD		Q, $CF_{1,2}$ vary with respiration; CF_{1-3} inverted; CR normal
25 (L. K.)	48	5'6"	179	LAD	normal	
26 (E. C.)	41	5'4"	192	LAD	Q_3, P_3, T_3 inverted	V_{1-6} low, CF_1 inverted
27 (K. W.)	18	5'6"	184	None	T_3 inverted	CF_1 inverted
28 (F. G.)	38	5'3"	196	LAD	Q_3, P_3, T_3 inverted	V_{1-6} low, CF_1 inverted, CF_2 diphasic, $CF_{3,4}$ low; $CL_{1,2}$ inverted, CL_3 diphasic, CL_{4-6} low
29 (R. M.)	40	5'4"	184	LAD	P_3, T_3 inverted	CF_1 inverted
30 (L. A.)	48	5'4"	160	LAD		CF_{1-6} low or inverted
31 (B. A.)	56	5'2"	162	LAD	Q_3	
32 (R. G.)	46	5'3"	166	None		CF_1 inverted, V_1 low
33 (L. C.)	41	5'2"	220	LAD	Q_3, P_3, T_3 inverted	V_{1-6}, CF_{1-6} low; CL_{1-4} inverted or diphasic; $CL_{5,6}$ isoelectric
34 (M. K.)	25	5'2"	250	LAD	Q_3, T_3 inverted	CF_1 inverted, V_{2-6}, CF_{2-6} low; $CL_{1,2}$ inverted, CL_3 isoelectric, CL_{4-6} low

cardiogram and a negative extremity potential has a "positive" influence. Thus, in normal persons a positive T wave in the unipolar left arm lead (aV_L) exerts a negative influence or subtracts from the positive voltage of the T wave in CL leads. Conversely, the normally negative T wave in the unipolar right arm lead (aV_R) has a positive effect on the T wave of the chest leads and increases the size of the T wave in the CR leads. As Hecht[13] pointed out, in normal persons the T wave in the precordial leads in Positions 2 through 6 as a rule is of sufficient amplitude so that the extremity influences do not produce inversion of this wave. The common terminal of Wilson is presumably nearly neutral, nullifying the extremity influences; when it is used as the indifferent electrode the exploring electrode should reflect the electrical changes taking place directly beneath it. Since there is considerable discussion concerning the validity and usefulness of unipolar leads,[14] in the present investigation they were compared with the CF, CR, and CL leads in order to determine whether the extremity potentials significantly distort the precordial electrocardiogram in obesity.

MATERIAL

Thirty-four of forty-seven markedly obese women attending the nutrition clinic were studied consecutively. The remaining thirteen were excluded after preliminary examination revealed hypertension or evidence of cardiac disease. In the thirty-four patients retained there were no symptoms or signs of cardiac disease or hypertension; in addition, fluoroscopy, x-ray examination of the chest in the posteroanterior and oblique positions, and the electrocardiogram after a standard two-step exercise test were normal. The average age, weight, and height of the patients were, respectively, 43 years, 201 pounds, and 5 feet, 4 inches (Table I). The weight of the patients was relatively constant except in one who lost 20 pounds.

METHOD

The three standard leads and the CF leads in the six official positions were recorded in each patient in the sitting position. In twelve patients the CR, CL, unipolar chest (V), and augmented unipolar extremity (aV) leads were also obtained. When the sitting electrocardiogram showed variations from normal, it was repeated in the recumbent position and during inspiration and expiration.

RESULTS

Eighty-five per cent of the patients showed a mild or moderate degree of left axis deviation in the standard leads; that is, the main deflection of the QRS deviation was directed upward in Lead I and downward in Lead III (Table I). Five patients (15 per cent) showed a Q_3 and inverted T_3. Six patients (18 per cent) showed inverted P_3 in addition to Q_3 and inverted T_3. In four patients (12 per cent) P_3 and T_3 were inverted but there was no Q_3. Thus, 45 per cent of the patients presented a typical pattern of obesity in Lead III in addition to simple left axis deviation. In two patients (6 per cent) T_1 and T_2 were less than 1.0 mm. high during one phase of respiration (Fig. 1). A Q wave was not

present in Lead II in any case. One patient showed a small Q wave in Leads CF_1, CF_2, and CF_3 which disappeared with respiration. Another patient revealed a Q wave in Leads CF_1 and CF_2 which did not vary with respiration. This finding is not unusual normally in these positions in CF leads.

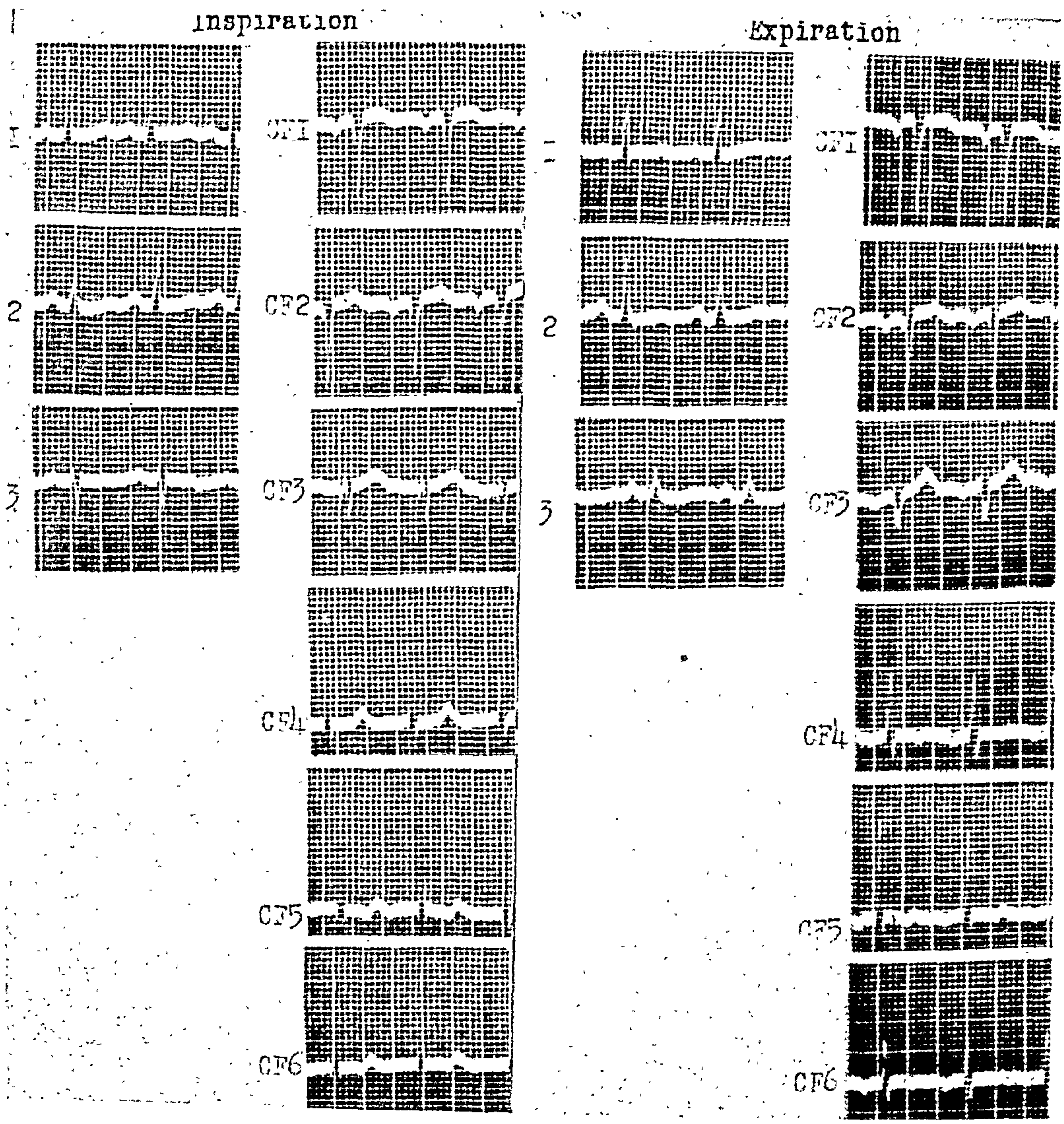


Fig. 1.—S. J., a 43-year-old woman, 5 feet 7 inches tall, weighed 230 pounds. Inspiration: There is left axis deviation, T_2 and T_3 are low, there is a Q wave in CF_1 and CR_2, and the T waves is CF_5 and CF_6 are diphasic. Expiration: There is no axis deviation, T_1 is low, and the T waves in CF_4 CF_5, and CF_6 are semi-inverted.

The QRS complex showed a small R wave in Lead CF_1 which gradually increased in size until Lead CF_5 and then diminished slightly in CF_6. The S wave was large in Lead CF_1, increased slightly in CF_2, and then gradually diminished

in intervening leads to CF_6, where it was 1.0 millimeter in height. The average heights of the waves in millimeters were as follows: In CF_1, R was 1.7 and S was 7.6; in CF_2, R was 2.7 and S was 7.7; in CF_3, R was 4.4 and S was 5.6; in CF_4, R was 8.3 and S was 4.5; in CF_5, R was 9.3 and S was 2.0; in CF_6, R was 8.3 and S was 1.0. These figures are considerably lower than those reported in normal subjects[3,4]; in our cases the R wave was almost 50 per cent smaller in Leads CF_1, CF_2, and CF_3 and 33 per cent smaller in CF_4 and CF_5. Furthermore, the R wave reached its greatest height (transition zone) in Lead CF_5 in our series and in CF_4 in normal persons. The S wave in Leads CF_1, CF_2, CF_3, and CF_4 also was only one-half as large in our series as in normal subjects. The height of the R wave in the V leads approximated that in the CF leads and was also definitely lower than the reported height in normal persons.[15]

Ninety-two per cent of the cases showed T-wave inversion in Lead CF_1. This is greater than the incidence of 70 per cent inverted or diphasic T waves found in this position in normal subjects.[3,4] In Leads CF_2 and CF_3 T was inverted in ten cases (21 per cent), in three of which the inversion varied with respiration. Usually the T wave was upright in expiration and inverted in inspiration (Fig. 1). In Leads CF_4 and CF_5 T was inverted in four cases (12 per cent), in one of which it varied with respiration, and very low in three cases. In Lead CF_6 T was also inverted in four cases (12 per cent), in two of which it varied with respiration, and very low in two cases. The average amplitude of the upright T was 1.2 mm. in CF_1, 1.32 mm. in CF_2, 1.8 mm. in CF_3, 2.2 mm. in CF_4, 1.8 mm. in CF_5, and 0.88 mm. in CF_6. These figures are less than 50 per cent of those reported in normal persons.[3,4] It is noteworthy that in two cases presenting T-wave inversion in the CF leads there was no axis deviation in the standard leads and P_3 and T_3 were upright.

The CR leads showed upright T waves in all positions except in one patient in whom T was diphasic in Leads CR_4, CR_5, and CR_6. The T wave was always taller than in the CF, CL, and V leads.

The CL leads showed deviation of the T wave in three (25 per cent) of the twelve cases recorded; T was inverted in CL_1 and CL_2, diphasic or isoelectric in CL_3 and CL_4, and low in CL_5 and CL_6. In these three cases the T waves were low in the CF and V leads (Figs. 2 and 3).

The V precordial leads showed low T waves (less than 1.0 mm.) in four cases (33 per cent) but the T wave was not inverted except in Position 1. The average height of T was as follows: in Lead V_1, -0.8 mm.; in V_2, 2.0 mm.; in V_3, 2.2 mm.; in V_4, 2.4 mm.; in V_5, 2.2 mm.; and in V_6, 1.5 millimeters. These values are less than one-half those reported in normal subjects.[15] This was also true of the R wave.

The augmented unipolar extremity leads presented considerable variation of the T wave. In Lead aV_L this wave was high in two cases, normal in two cases, low or isoelectric in seven, and diphasic in one case. In Lead aV_F it was high in five cases, normal in three, low in three, and diphasic in one case. In Lead aV_R the T wave was always inverted except in one case in which it was isoelectric.

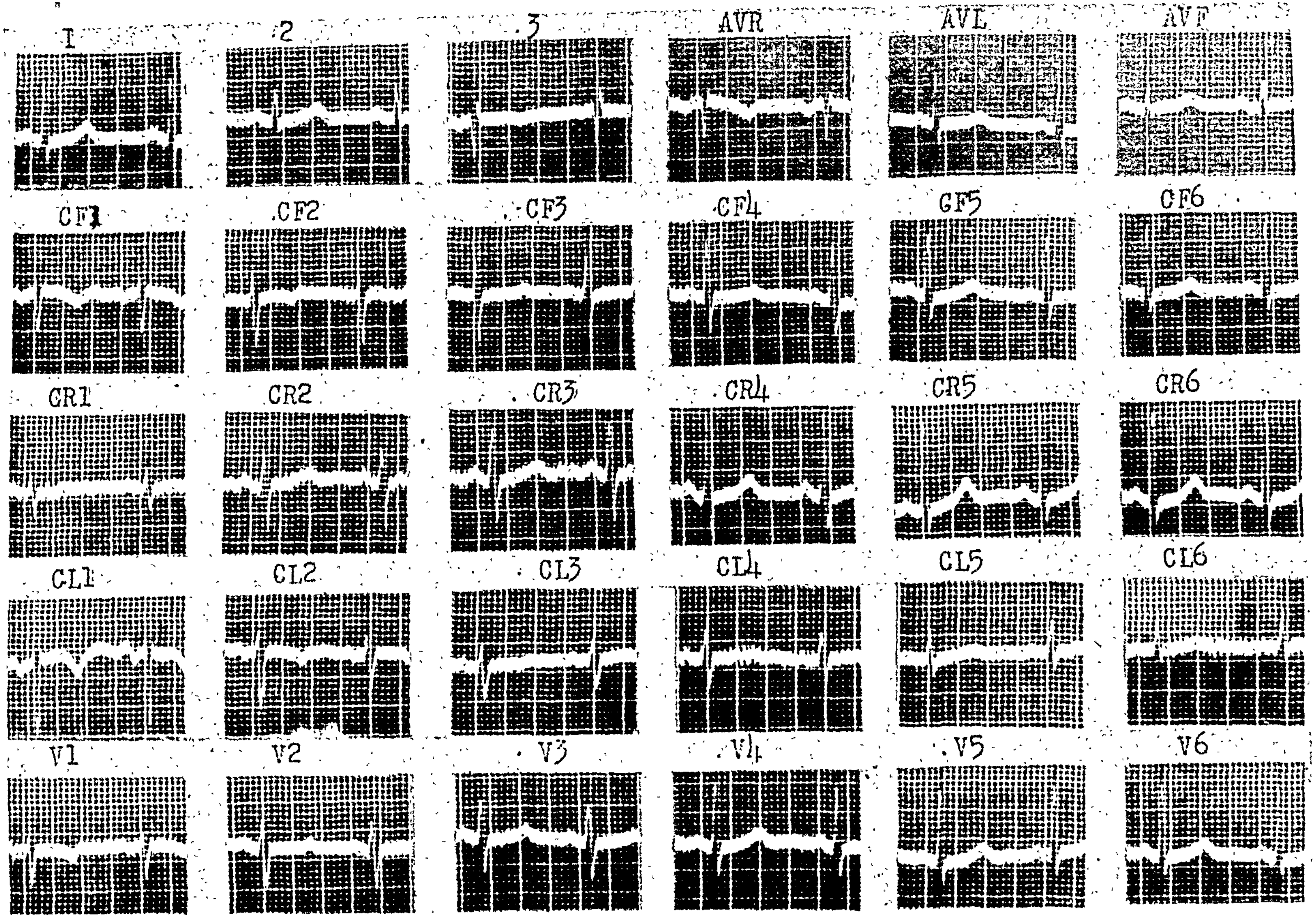


Fig. 2.—R. G., a 46-year-old woman, 5 feet 3 inches tall, weighed 166 pounds. CF leads are within normal limits, showing inverted T wave in Position 1 and diphasic T in Position 2. CL leads show inverted T waves in Positions 1 and 2 and isoelectric T waves in Positions 3, 4, 5, and 6. CR leads are normal. V leads show normal but relatively low T waves in Positions 2 to 6. The T wave in aV_L and aV_F is upright and is greater in aV_L. This accounts for the greater distortion of the CL than the CF leads.

Case 17, in which the T wave had originally been inverted in Leads CF_1, CF_2, CF_3, CF_4, and CF_5, was re-examined five months later after the patient had lost 20 pounds. At this time all of the CF, CR, CL, and V leads were normal (Fig. 4).

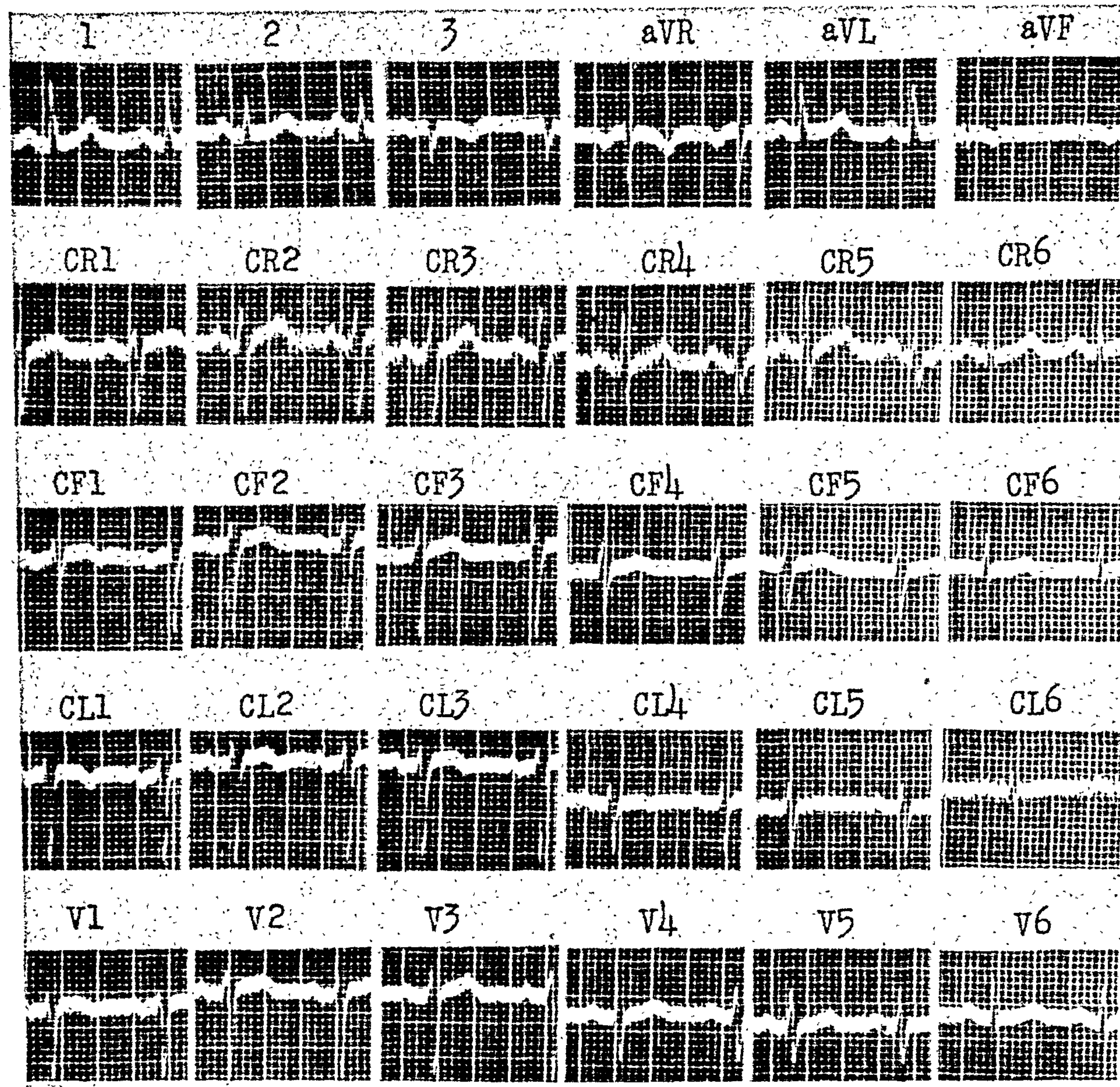
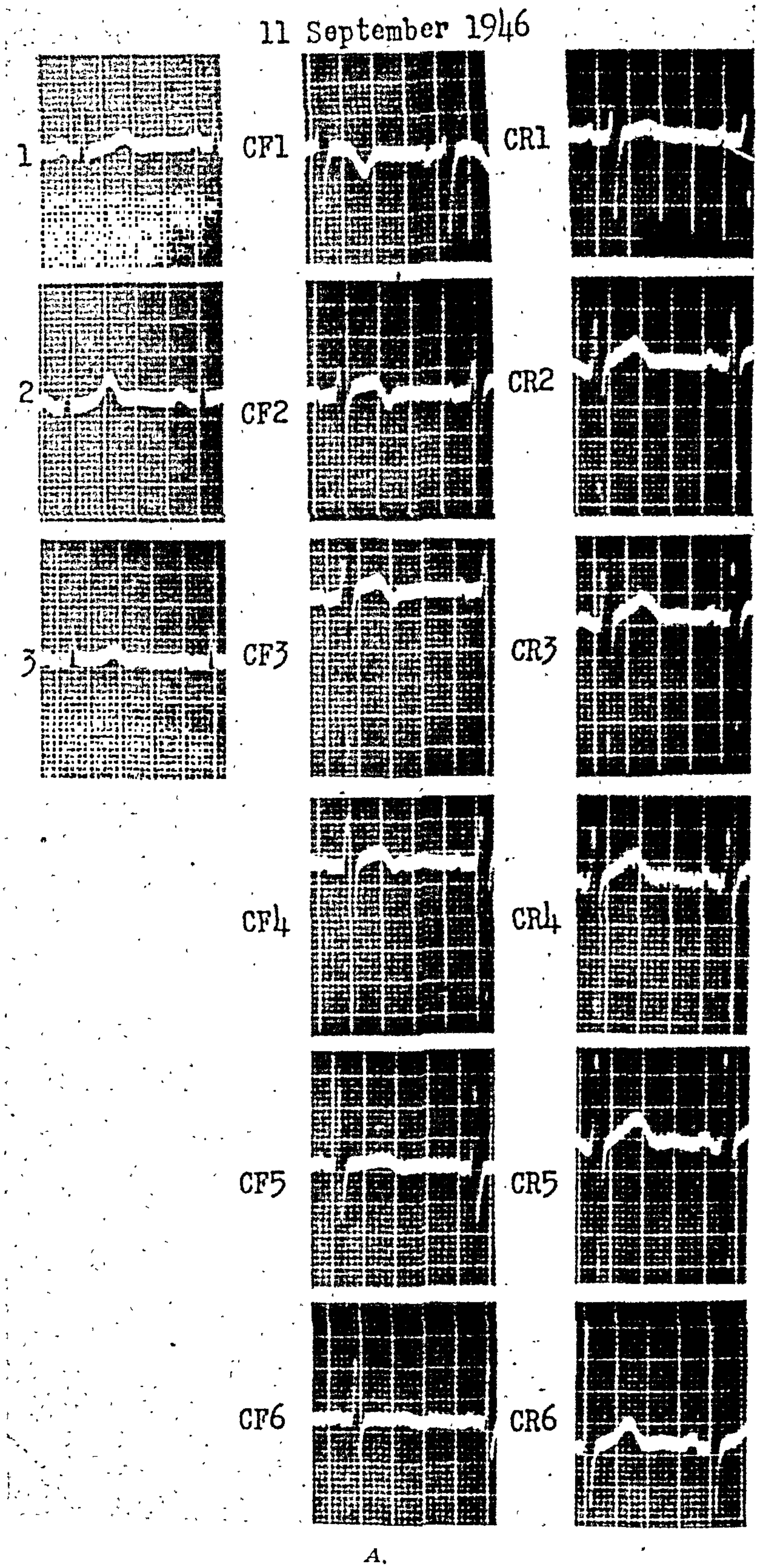


Fig. 3.—L. C., a 41-year-old woman, 5 feet 2 inches tall, weighed 220 pounds. CR leads are normal. CF and V leads are normal and similar, the T waves being relatively low. CL leads show diphasic T waves in Positions 1 to 4 and isoelectric T waves in Positions 5 and 6. Lead aV_L shows upright T wave, accounting for the distortion of CL. In aV_F the T is inverted, but low; therefore, the CF leads are not disturbed.

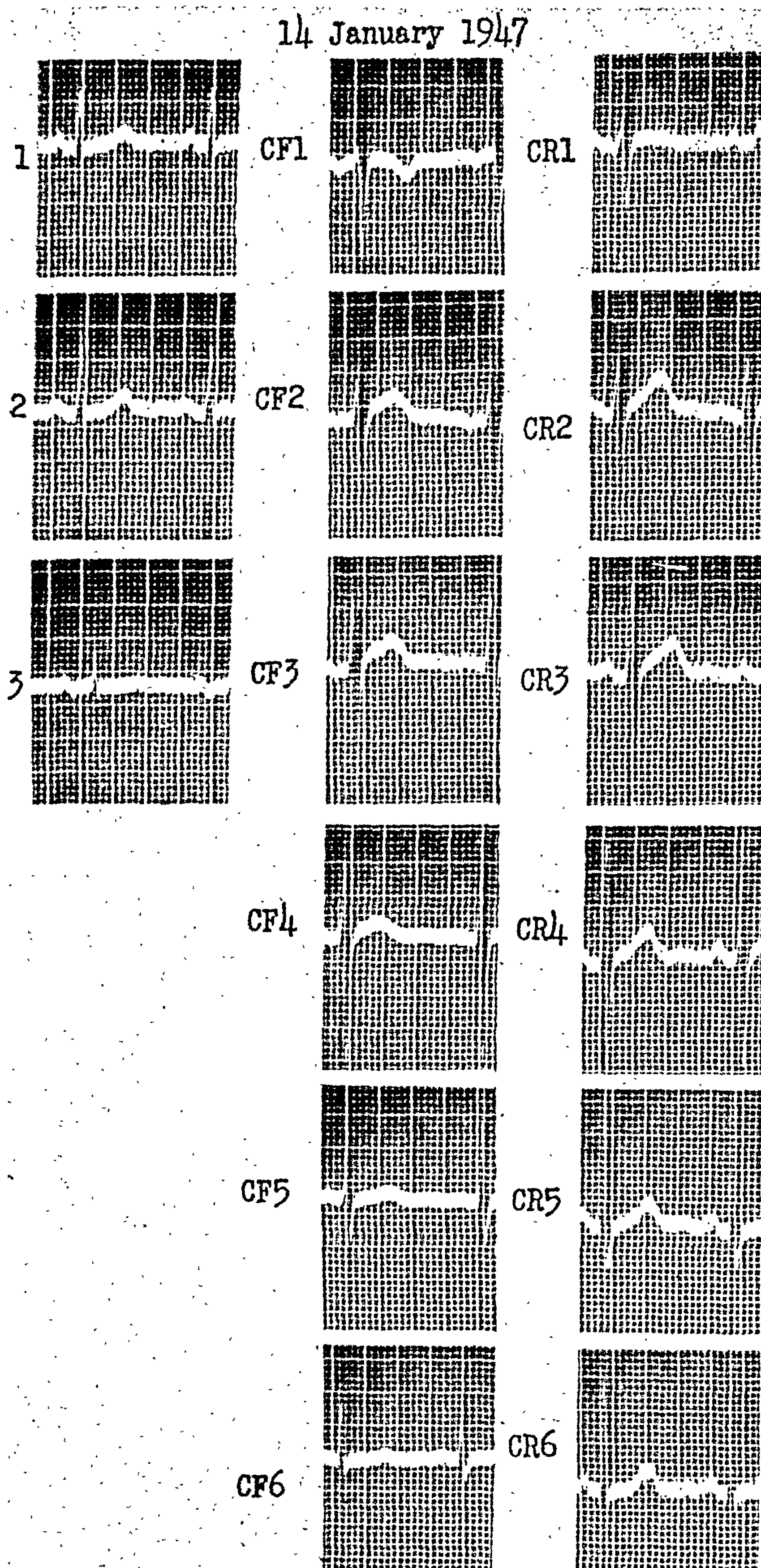
DISCUSSION

It is apparent that in obesity the T wave, as measured in precordial V leads, is distinctly reduced in amplitude and that, as a result, the influences of the left arm and leg may be great enough to produce further lowering or inversion of the T wave in the CF and CL leads. This does not occur in the CR leads since the T wave is normally negative in Lead aV_R and thus exerts a positive influence on



A.

Fig. 4.—E. S., a 50-year-old woman, 5 feet 2 inches tall, weighed 187 pounds. *A*, Sept. 11, 1946: CR leads normal. CF leads show diphasic T waves in all positions. *B*, Jan. 14, 1947, following loss of 20 pounds: CF leads are normal.



B.

Fig. 4 (Cont'd).—See opposite page for legend.

the precordial T wave. In Leads aV_L and aV_F the T wave is positive and therefore tends to invert the T wave in the CL and CF leads. Since the precordial T wave is frequently very low in obese persons, the T wave may be isoelectric or inverted in the CL and CF leads even when the T wave in Leads aV_L and aV_F is of normal or low amplitude.

That the T-wave inversion in the CF and CL leads in our cases was not significant is evident from the negative clinical findings, namely, the absence of changes in the electrocardiogram after two-step exercise[16] and the disappearance of the inversion during respiration in one-half the cases and after loss of weight in Case 17. Therefore, the usual interpretation of inversion of the T wave in the CF and CL leads as abnormal does not hold in obese persons; in them V leads are more reliable and should be employed. Our findings thus confirm the suggestion of previous writers[11,13] that distortion effects from the extremity potentials may produce false positives in the CF and CL leads. In addition to the T-wave inversion found in obese persons, we have occasionally observed in other patients a false Q wave in CF leads which was not present in the V leads. It is, therefore, probable that if a single chest lead is to be recorded routinely, the V lead is preferable.

Several authors have suggested that in certain conditions the distortion effects inscribed in the CF and CL leads may be of additional value.[6,13] We have observed a case of coronary occlusion in which a Q wave was present in the CF leads but not in the V leads and occasional cases of acute hemorrhage in which T-wave changes were present only in the CL of CF leads.[17] However, it must be realized that these are distortion effects which are to be evaluated in relation to the unipolar chest and extremity leads. It is our impression that the standard leads and the unipolar chest and extremity leads furnish complete information, but this point requires further investigation in various conditions. It has been stated[12] that CR leads are preferable to the other chest leads. This is true in normal persons, since the CR leads are distorted by the positive influence of the right arm potential and record increased height of the T waves. Thus, these leads do not show the lowering of the T wave seen in obese persons in the other chest leads. However, in abnormal conditions, CR leads may mask T-wave abnormalities.

There are several possible mechanisms by which the amplitude of the precordial T wave is reduced in obese persons. The most likely is clockwise rotation of the heart as a result of elevation of the diaphragm. This causes the right ventricle to face forward and the left ventricle to face backward, thus reducing the precordial electrical potential since the strong left ventricle potential is directed posteriorly. Recently we have clearly observed the influence of the position of the diaphragm on the standard precordial leads in a case of cirrhosis of the liver with ascites (Fig. 5). Prior to removal of the fluid from the peritoneal cavity, the electrocardiogram showed isoelectric T waves in Leads II and III and all chest leads. Following paracentesis the T wave became upright in all leads. Later, post-mortem examination revealed the heart to be normal, and thus the changes in the electrocardiogram were secondary to the alteration in the position of the heart; the heart was situated transversely prior to para-

centesis and normally after it. The disappearance of T-wave inversion in the CF leads in one of our patients following a weight loss of 20 pounds may also be explained in this way. Wallace and associates[18] have suggested that the conducting tissues surrounding the heart are altered when the diaphragm is elevated, resulting in a reduction in the chest potential. A third possible explanation is the thickness of the chest wall in obese persons. However, this factor is not present in pregnancy and ascites in which identical changes occur in the electrocardiogram.

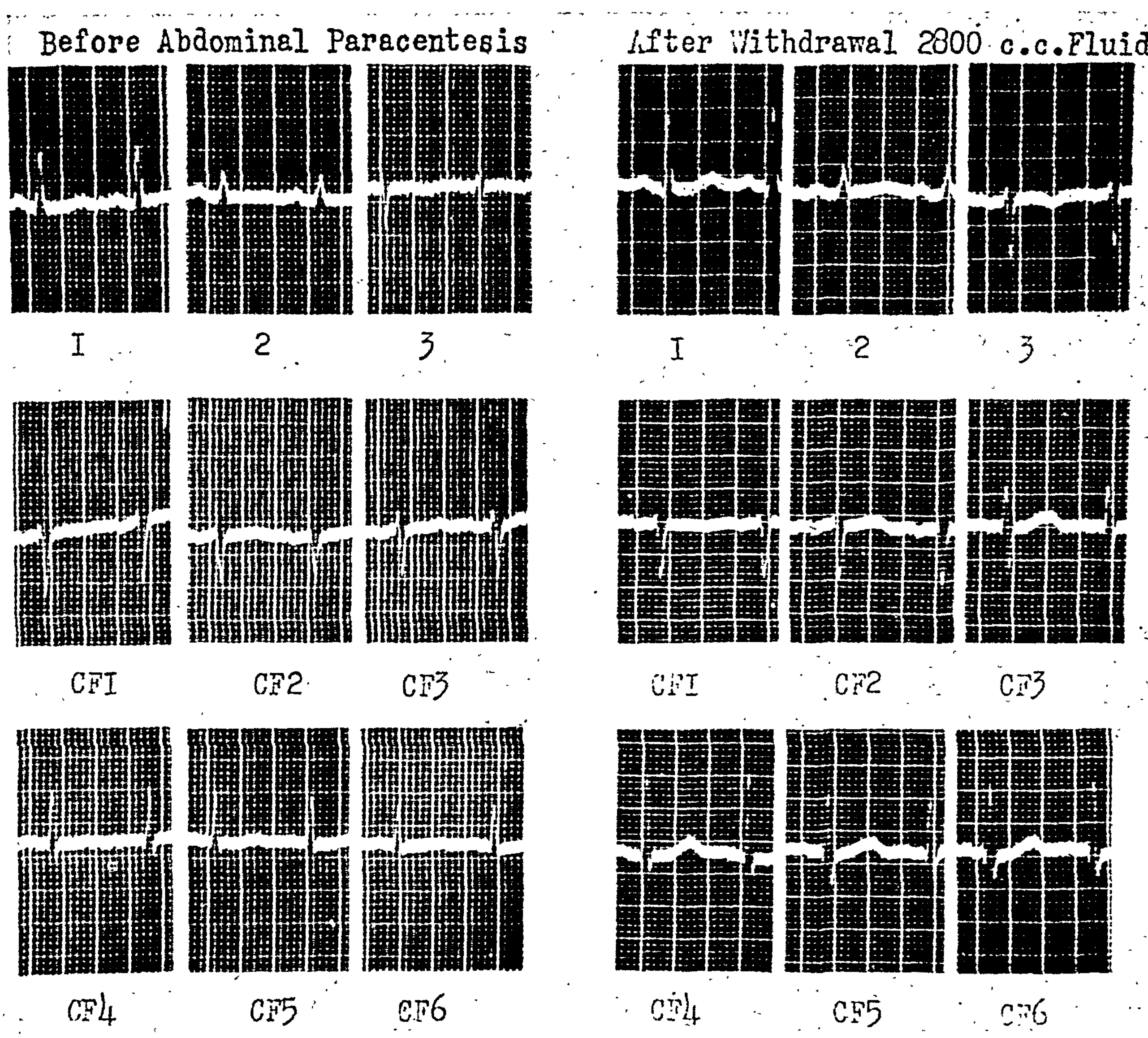


Fig. 5.—J. F., a 50-year-old man with cirrhosis of liver with ascites. Before paracentesis: T waves isoelectric or low in all standard and CF leads. This is the result of elevation of the diaphragm. After paracentesis: T waves are within normal limits.

SUMMARY

Obesity is often associated with a Q wave and inversion of T in standard Lead III, changes which may simulate myocardial involvement and posterior infarction. The present investigation was undertaken to determine whether significant changes occurred in the chest leads.

In obesity the amplitude of the precordial T wave, as measured in the unipolar (V) leads, is reduced to 50 per cent of normal. However, the T wave was not inverted in the V leads recorded in Positions 2 through 6.

The extremity influences may be great enough to produce significant distortion of the T wave in CF and CL leads. In these leads the T wave was inverted in leads made in Positions 2 and 3 in 20 per cent of the cases of our series, and in leads made in Positions 4, 5, and 6 in 10 to 15 per cent. An inverted T wave in the CF and CL leads obtained from obese subjects is not abnormal. The CR leads show distortion in the direction of normality. This is useful in obesity but may mask T-wave alteration in abnormal conditions.

The diminished height of the precordial T wave in obese subjects is probably the result of elevation of the diaphragm. In support of this view, a case of ascites with T-wave changes in the CF leads is described in which the T waves became normal following paracentesis.

The unipolar chest (V) leads should be employed routinely since they are probably more reliable than the CF, CL, and CR leads.

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ELECTROCARDIOGRAPHIC CHANGES DURING ANTHIOMALINE TREATMENT OF SCHISTOSOMIASIS

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SAN JUAN, P. R.

SEVERAL papers have appeared in recent years dealing with the effect of the antimony compounds on the electrocardiogram. Mainzer and Krause[1] observed twelve patients; Magalhaes and Dias[2] studied twenty-one; Tarr,[3] sixty-six; Beaser and Rodriguez Molina[4] reported on twenty-five, and Schroeder, Rose, and Most[5] told of their observations on 100 cases. These investigators used either tartar emetic or Fuadin, or both drugs, and their series included cases of *Schistosoma japonicum* and *Schistosoma mansoni*.

We have chosen for this report twenty cases of a series of over 120 cases of *Schistosoma mansoni*, which have been treated with Anthiomaline. The twenty cases were all male subjects, ranging in age from 12 to 56 years, with an average age of 25.3 years, in whom there was no clinical evidence of cardiovascular disease. Records were taken before treatment was instituted, again after the second injection, after the tenth, two weeks after the last injection, and, in some cases, a final record was taken three months later. Treatment consisted of fifteen injections given intramuscularly in doses of 3.0 c.c. every other day, except Sundays. The electrocardiographic tracings were obtained in the morning hours, usually one hour after the injection, with the patient in the supine position. The three standard leads, the unipolar limb leads, and six precordial leads, using Wilson's central terminal, were taken.

There are three antimony compounds most commonly used in the treatment of schistosomiasis and all are trivalent:

Tartar emetic (sodium and potassium tartrate). A freshly made 0.5 per cent solution is given intravenously in doses of 5, 10, and 15 c.c. on the first, third, and fifth days, and subsequently 20 c.c. every other day until a total of 210 c.c. has been given. The entire course of treatment lasts thirty-one days. The amount of the drug administered is 1.45 Gm., which represents 0.522 Gm. of antimony.

Fuadin (sodium antimony pyrocatechin sulfonate). A 6.3 per cent solution is given intramuscularly in doses of 1.5 c.c., 3.5 c.c., and 5.0 c.c. on three suc-

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The Anthiomaline used in this investigation, and in the treatment of over 120 cases of *Schistosoma mansoni*, was generously supplied by Dr. D. F. Robertson, Associated Medical Director of Merck & Co., Inc., Rahway, N. J.

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cessive days, followed by 5.0 c.c. every other day for twelve injections until a total of 70 c.c. has been given. The amount of the drug administered is 4.48 Gm., which represents 0.599 Gm. of antimony.

Anthiomaline (antimony salt of lithium anthiomalate). A 6.0 per cent solution is given intramuscularly in doses of 3.0 c.c. every other day, until a total of 60 c.c. has been administered. The amount of the drug injected is 1.35 Gm. Anthiomaline contains 6.9 per cent of lithium and 20 per cent of antimony. One cubic centimeter of the solution is equivalent to 10 mg. of antimony. A full course of treatment, therefore, represents 0.450 Gm. of antimony.

In Mainzer and Krause's[1] series of twelve patients treated with tartar emetic, nine showed electrocardiographic alterations. In three of the nine, the changes were sufficiently abnormal to suggest "suspicion of an altered function of the cardiac muscle." They reported changes in P waves, which turned negative, became lower, or disappeared altogether; changes in T waves, which became lower, isoelectric, or inverted; changes in the S-T and T elements, which became "indistinctly separated and fused with one another"; and a persistent bradycardia during the course of antimony treatment. In their series there was a negative T_1 in one case, a negative T_2 in another, and a negative T_3 in five others. "The electrocardiographic abnormalities," they say, "as well as the bradycardia, are, therefore, considered as resulting from intoxication of the heart muscle through therapeutic antimony administration, though the process in most cases is not clinically evident. In exceptional cases, the condition may result in sudden death, through auricular fibrillation."

Tarr's[3] series of sixty-six patients showed that the electrocardiographic changes were more frequent in those receiving tartar emetic (31 per cent) than in those under Fuadin treatment (7 per cent). Some of the changes, he claims, were so striking that they might have been mistaken for evidences of myocardial damage, but the alterations in the electrocardiogram were limited almost entirely to the T waves. Changes in the P waves, P-R interval, QRS complex, and elevation or depression of the R-T or S-T segment were conspicuously absent, and no disturbances in rhythm were noted. Fig. I of his paper[3] shows negative T_1, T_2, T_3, and T_4, which "might easily have been interpreted as evidence of myocardial damage or even coronary occlusion."

Magalhães and Dias[2] reported similar T-wave changes in seven of fourteen of their recorded electrocardiograms. Beaser and Rodriguez Molina[4] found decrease in voltage of the T waves in twenty of their twenty-five patients receiving a course of Fuadin therapy, and recommended that "the course of Fuadin be spaced four or more weeks apart to avoid a cumulative effect upon the myocardium, even though that effect is probably reversible in nature."

Schroeder, Rose, and Most[5] reported an increased amplitude of P waves in Leads II and III in 11 per cent of their cases and a fusion of RS-T segment and T waves in 45 per cent of them. Varying degrees of decrease in amplitude of T waves in all leads with inversion in many cases was reported in 99 per cent of the patients, the changes being more pronounced during tartar emetic than during Fuadin treatment. There was a prolonged Q-T interval in 27 per cent.

They advise that "recent antimony therapy must be considered in evaluating abnormal electrocardiograms found in veterans, and others."

The electrocardiographic alterations have been attributed to the effect of antimony on the heart muscle, although experimentally, in dogs, it has been found that antimony, at least urea stibamine,[6] has no immediate effect upon the electrocardiogram; no lesions were found in the myocardium of dogs which died during the administration of large amounts of antimony.[5] Mainzer and Krause seem to favor vagus stimulation "by narrowing the coronary blood stream" as a possible explanation for antimony effect on the electrocardiogram. They say that there is "marked parallelism between the intensity of the bradycardia and the electrocardiographic changes." On the other hand, Magalhães and Dias attribute the effects of antimony "to dilatation of the capillaries of the coronary circulation with diminution in the effective circulation of the heart." The fact that there is pronounced difference between the effect brought on by tartar emetic and Fuadin and the further fact that the drugs differ also in their antimony values, as well as in the content of sodium and potassium ions, prompted the writers to investigate the electrocardiographic alterations produced by Anthiomaline, which contains no sodium or potassium, but lithium.

The changes induced by a regular course of tartar emetic, which represents the administration of 0.522 Gm. of antimony, are more marked than those observed during a regular course of Fuadin, which represents 0.599 Gm. of antimony. Such changes may point to the possibility that the toxic effect of the antimony molecule is not the sole agent responsible for the changes, unless it has to do with the route of administration. The potassium ions present in tartar emetic (and not in Fuadin) cannot be blamed for the electrocardiographic changes, as it has been shown that hyperpotassemia produces just the opposite change: an increase in T-wave amplitude and lowering and eventual disappearance of P waves.

RESULTS

Rhythm, Heart Rate, and $\hat{A}_{QRS}$.—There were no changes observed in cardiac rhythm, pulse rate, and $\hat{A}_{QRS}$ during Anthiomaline treatment. Table I shows that the number of patients with sinus rhythm and with sinus arrhythmia was

TABLE I. CARDIAC RHYTHM, PULSE RATE, AND $\hat{A}_{QRS}$ BEFORE TREATMENT, AFTER SECOND INJECTION, AND AFTER TENTH INJECTION

	BEFORE	SECOND RECORD	THIRD RECORD
Sinus rhythm	11	10	12
Sinus arrhythmia	9	10	8
Pulse rate			
Minimum	51	55	51
Maximum	81	100	80
Mean	61	69	63
$\hat{A}_{QRS}$			
Minimum	+ 5.0°	0.0°	+ 8.0°
Maximum	+108.0°	+105.0°	+100.0°
Mean	+ 55.9°	+ 54.7°	+ 55.0°

almost equally divided before treatment, after the second injection, and after the tenth injection. There were nine patients with sinus arrhythmia before treatment was started and only eight after the tenth injection. The mean heart rate was 61 per minute before treatment, 69 after the second injection, and 63 after the tenth. There was no bradycardia which could be attributed to therapy. $\hat{A}_{QRS}$ ranged from +5° to +108° before treatment, with an average of +55.9°; from 0° to +105°, with an average of +54.7° after the second injection; and from +8° to +100° after the tenth, with a mean $\hat{A}_{QRS}$ of +55°.

Limb Leads.—

P Waves: No changes were observed in the amplitude, contour, or duration of the P waves. Table II shows the amplitude of the P waves in Leads I, II, and III before treatment, after the second injection (second record), after the tenth injection (third record), and two weeks after treatment (fourth record). It also includes the number of diphasic, isoelectric, negative, and notched P waves encountered.

TABLE II. AMPLITUDE AND CONTOUR OF P WAVES

	LEAD I	LEAD II	LEAD III
Before			
Mean	0.80 mm.	1.28 mm.	0.88 mm.
Diphasic±	0	0	3
Isoelectric	0	1	2
Negative	0	0	2
Notched	2	2	1
Second record (after second injection)			
Mean	0.80 mm.	1.26 mm.	0.94 mm.
Diphasic±	0	0	2
Isoelectric	0	1	2
Negative	0	0	2
Notched	2	2	0
Third record (after tenth injection)			
Mean	0.81 mm.	1.28 mm.	0.87 mm.
Diphasic±	0	0	2
Isoelectric	0	0	1
Negative	0	0	2
Notched	0	2	0
Fourth record (two weeks after treatment)			
Mean	0.86 mm.	1.22 mm.	0.80 mm.
Diphasic±	0	0	3
Isoelectric	0	0	1
Negative	0	0	3
Notched	2	2	0

"Mean" figures represent voltage in millimeters. Other figures represent number of cases.

P-R Interval: The duration ranged from 0.10 to 0.18 second both before and during treatment, with an average of 0.15 second.

QRS Complex: No change in the amplitude, configuration, or duration of the QRS complex was observed. The mean duration was 0.07 second.

S-T Segment: This segment was neither depressed nor elevated during Anthiomaline treatment in Lead I. In Lead II it was found elevated in two instances: in one the elevation was +0.50 mm., originally, but went up to +1.00 millimeter. In Lead III, one patient showed elevation of +1.00 mm. and three others showed a depression of −0.50 mm. and −1.00 mm. following the second injection. The changes in S-T segment were so slight and rare that they could not be considered abnormal findings.

Q-T Interval: Table III shows the changes observed in electrical systole in the three standard leads during treatment with Anthiomaline; an increase occurred in the Q-T interval of all leads, but this increase was more pronounced after the tenth injection (third record). Two weeks after cessation of treatment, the Q-T interval had not returned to its original figure.

TABLE III. Q-T INTERVAL BEFORE TREATMENT, AFTER THE SECOND INJECTION, AFTER THE TENTH INJECTION, AND TWO WEEKS AFTER TREATMENT

	BEFORE (SEC.)	SECOND RECORD (SEC.)	THIRD RECORD (SEC.)	FOURTH RECORD (SEC.)
Lead I				
Minimum	0.28	0.32	0.32	0.32
Maximum	0.36	0.40	0.40	0.40
Mean	0.340	0.345	0.357	0.351
Lead II				
Minimum	0.32	0.32	0.32	0.32
Maximum	0.48	0.44	0.48	0.44
Mean	0.354	0.360	0.367	0.364
Lead III				
Minimum	0.32	0.32	0.32	0.32
Maximum	0.38	0.40	0.48	0.44
Mean	0.344	0.354	0.362	0.362

In Lead I, thirteen patients showed an increase, three showed a diminution, and four showed no alteration in the Q-T interval. In Lead II, ten patients showed an increase, four showed a diminution, and six suffered no change in the duration of the electrical systole; in Lead III there were thirteen patients with increased Q-T interval, but seven suffered no change in its duration.

T Waves: Table IV shows the changes observed in the amplitude and contour of the T waves in the three standard leads. The mean amplitude of the T waves showed a gradual diminution after the second and tenth injections, and a tendency to increase back to its control figure when the fourth record was obtained. Eighteen patients (90 per cent) exhibited a decrease in voltage, and in two records we observed the amplitude of the T wave to increase following the second injection, only to decrease at the tenth.

In Lead I no instance of a negative T wave was encountered either before or during Anthiomaline therapy. In Lead II a negative T wave, present before treatment, became more deeply inverted during treatment. In Lead III there

were two diphasic and three negative T waves before treatment; the same number of diphasic and six negative T waves following the second injection; three diphasic, one isoelectric, and eight negative T waves were present after the tenth injection. Two weeks after treatment, there were only one diphasic, three isoelectric, and four negative T waves in Lead III.

TABLE IV. CHANGES IN THE T WAVES

	LEAD I	LEAD II	LEAD III
Before			
Mean	2.52 mm.	3.69 mm	1.48 mm.
Diphasic ∓	0	0	2
Isoelectric	0	0	0
Negative	0	1	3
Second record (after second injection)			
Mean	2.43 mm.	2.84 mm.	1.23 mm.
Diphasic ∓	0	0	2
Isoelectric	0	0	0
Negative	0	1	6
Third record (after tenth injection)			
Mean	2.08 mm.	2.06 mm.	1.03 mm.
Diphasic ∓	0	0	3
Isoelectric	0	0	1
Negative	0	1	8
Fourth record (two weeks after treatment)			
Mean	2.23 mm.	2.85 mm.	1.33 mm.
Diphasic ∓	0	0	1
Isoelectric	0	0	3
Negative	0	1	4

In Lead III upright T waves in the control records became negative in four instances; another became diphasic. One which was originally diphasic became negative, and the other diphasic wave underwent no change. Two negative T waves became more pronounced, and the other negative T wave became less pronounced in the third record and isoelectric in the fourth. Most of the changes occurred, therefore, in Lead II, but the alterations observed in the standard leads were never sufficiently pronounced to suggest myocardial or coronary disease.

Precordial Leads.—In the chest leads, observations were limited to the P-R interval, duration of the QRS complex, the Q-T interval and the S-T segment, and to a study of the P and T waves in the six precordial leads. Table V shows that there were no alterations in the P-R interval or in the duration of the QRS complex.

P Waves: The small P waves in the precordial leads normally diminish in amplitude when the exploring electrode is moved to the left side of the chest. The mean amplitude in this series being 0.359 mm. in Lead V_1 and only 0.138 mm. in Lead V_6, there is, consequently, an increased number of isoelectric P waves in the latter lead (six cases with none in V_1). The mean amplitude of the

P waves was slightly less in Leads V_1 and V_2, but somewhat higher in the other four precordial points after the second injection (second record in Table V). After the tenth injection (third record), the amplitude of the P waves increased slightly in leads made at precordial Positions 1, 2, 3, and 5, but diminished in leads made at Positions 4 and 6. When the fourth record was taken, in none of the cases had the P waves returned to its control figure. The most pronounced changes in amplitude and contour of the P waves were, of course, observed in Lead V_1.

TABLE V. CHANGES IN THE P WAVES IN PRECORDIAL LEAD

	V_1	V_2	V_3	V_4	V_5	V_6
Before						
Mean	0.359 mm.	0.302 mm.	0.209 mm.	0.252 mm.	0.189 mm.	0.138 mm.
Isoelectric	0	0	2	1	3	6
Diphasic±	1	0	0	0	0	0
Negative	1	0	0	0	0	0
Second record (after second injection)						
Mean	0.330 mm.	0.288 mm.	0.214 mm.	0.251 mm.	0.215 mm.	0.170 mm.
Isoelectric	3	3	5	2	3	6
Diphasic±	2	0	0	0	0	0
Negative	0	0	0	0	0	0
Third record (after tenth injection)						
Mean	0.446 mm.	0.324 mm.	0.287 mm.	0.204 mm.	0.201 mm.	0.133 mm.
Isoelectric	2	0	0	2	4	6
Diphasic±	1	0	0	0	0	0
Negative	0	0	0	0	0	0
Fourth record (two weeks after treatment)						
Mean	0.389 mm.	0.330 mm.	0.289 mm.	0.184 mm.	0.155 mm.	0.120 mm.
Isoelectric	1	1	1	3	2	5
Diphasic±	3	0	0	0	0	0
Negative	0	0	0	0	0	0

P-R interval = 0.10 – 0.18 sec. Av. 0.152 sec.
QRS duration = 0.04 – 0.10 sec. Av. 0.083 sec.

T Waves: The amplitude and contour of the T waves of the precordial Leads appear in Table VI. There was a definite decrease in amplitude of the T waves observed during Anthiomaline treatment with a tendency to return to the control figures two weeks after treatment.

Before treatment, there were five diphasic T waves in Lead V_1, one in Lead V_2, and one in Lead V_3, and two negative T waves in Lead V_1 and one in Lead V_2.

After the second injection of Anthiomaline there were three negative T waves in V_1, one in V_2, and one in V_3; the diphasic T waves suffered no alterations, except that one appeared in Lead V_1. After the tenth injection, the number of negative T waves increased to five in V_1, one in V_2, one in V_3, two in V_4, one in V_5, and one in V_6. Two weeks after treatment, there were six negative T waves in Lead V_1, one in V_2, one in V_3, and two in Lead V_4.

TABLE VI. CHANGES IN T WAVES IN PRECORDIAL LEADS

	V_1	V_2	V_3	V_4	V_5	V_6
Before						
Mean	1.55 mm.	3.15 mm.	3.60 mm.	3.56 mm.	3.30 mm.	2.55 mm.
Diphasic±	5	1	1	0	0	0
Negative	2	1	0	0	0	0
Second record (after second injection)						
Mean	1.58 mm.	2.79 mm.	3.01 mm.	2.88 mm.	2.66 mm	2.02 mm.
Diphasic±	5 (1∓)	1	0	0	0	0
Negative	3	1	1	0	0	0
Third record (after tenth injection)						
Mean	1.35 mm.	1.93 mm.	2.54 mm.	2.26 mm.	2.0 mm.	1.64 mm.
Diphasic±	5	1	1	0	0	0
Negative	5	1	1	2	1	1
Fourth record (two weeks after treatment)						
Mean	1.37 mm.	2.35 mm.	3.02 mm.	2.63 mm.	2.32 mm.	1.98 mm.
Diphasic±	4	4	1	0	0	0
Negative	6	1	1	2	0	0

A boy, 12 years of age, showed negative T waves in V_1, V_2, V_3, and V_4 following the tenth injection when the control record showed negative T waves only in V_1 and V_2 (Fig. 1). A man, 24 years of age, who originally showed only diphasic T waves in V_1, showed negative T waves at all six precordial points after the tenth injection (Fig. 2).

The amplitude of the T waves decreased during Anthiomaline treatment in eighteen of the twenty patients (90 per cent). In four cases, however, an increase in amplitude of the T waves after the second injection was found. In one case, in Lead V_3, the T waves, two weeks after treatment, were 6.0 mm. when the control amplitude had been only 3.25 mm., having gone down to 1.50 mm. during therapy; also in another case the amplitude of the T wave was higher after (3.75 mm.) than before (2.25 mm.) treatment.

The S-T Segment: This portion of the ventricular complex was found on the isoelectric line in 60 per cent of the cases and from 0.5 to 1.0 mm. above the isoelectric line in 40 per cent. When it was above the isoelectric line, the control record was also slightly elevated. In Lead V_1 only four patients showed elevation. In Lead V_6 only one showed elevation. These were normal findings.

Q-T Interval: In the precordial leads, the electrical systole suffered a slight prolongation, similar to that observed in the three standard leads. For the sake of brevity, we are giving the figures for only Lead V_5 (Table VII).

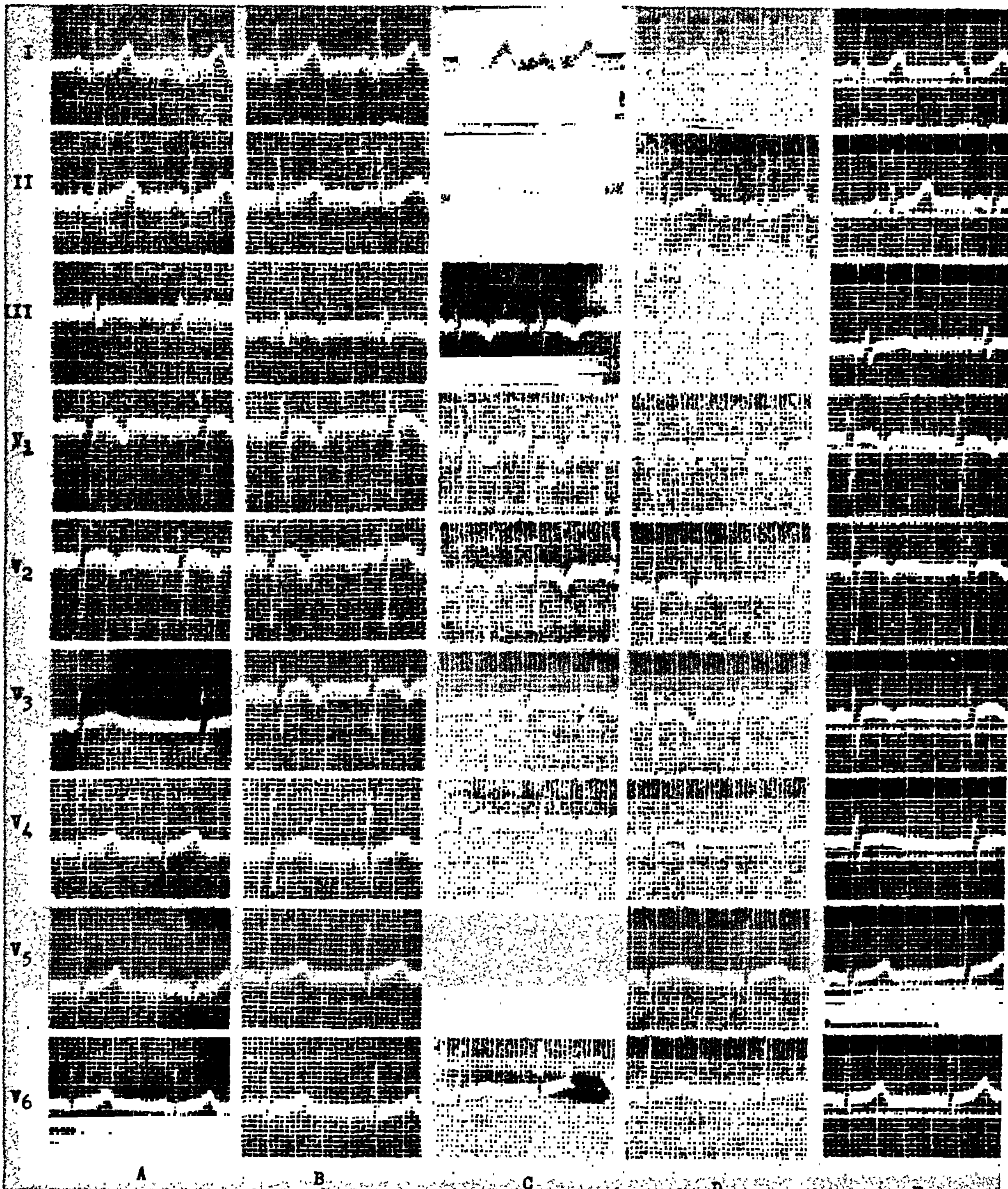

Fig. 1.—B. P. (Case 2025), 12 years of age. *A*, control record; *B*, after second injection; *C*, after tenth injection; *D*, two weeks after treatment; *E*, three months after treatment.

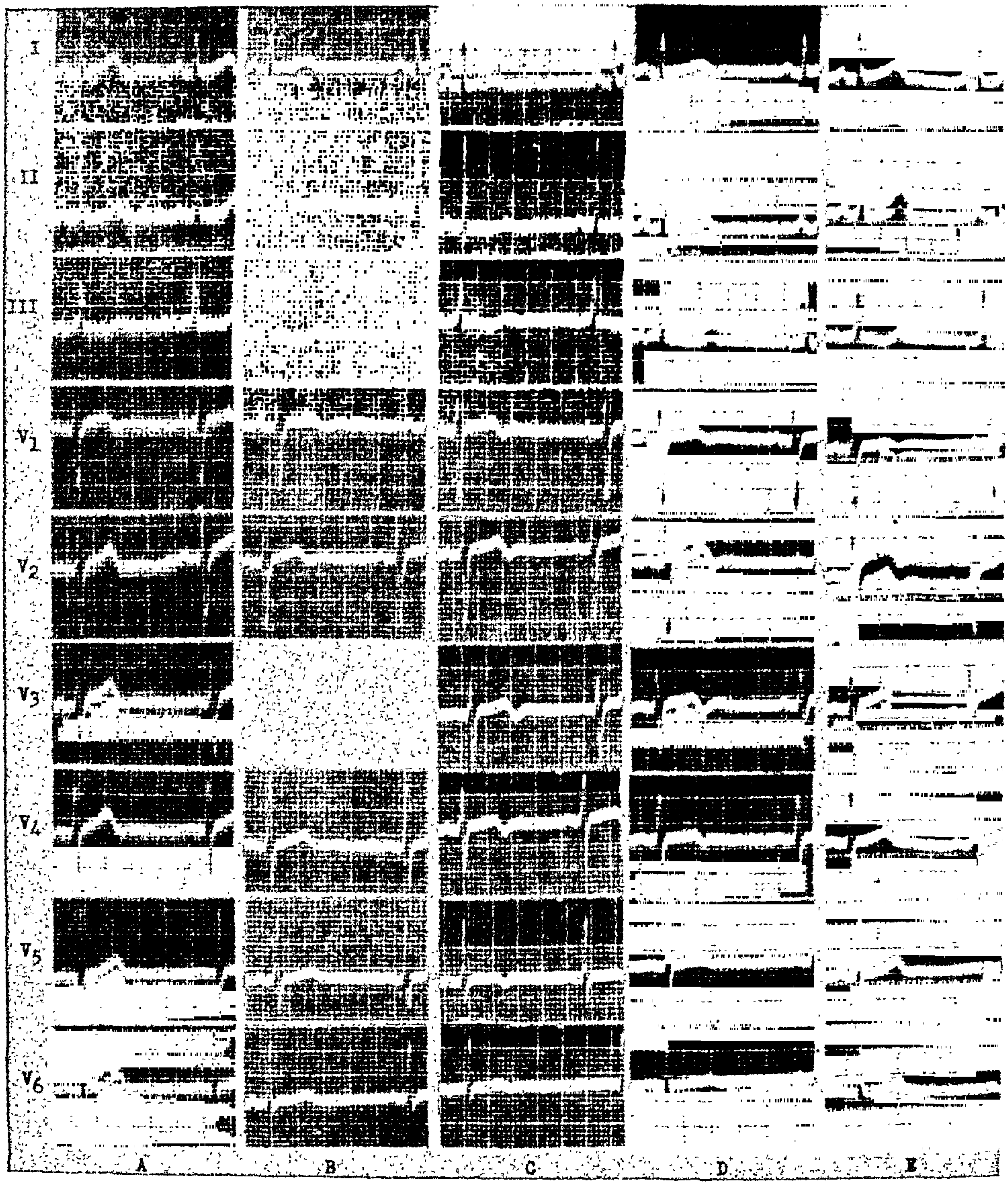

Fig. 2.—J. S. (Case 7080), 24 years of age. *A*, control record; *B*, after second injection; *C*, after tenth injection; *D*, two weeks after treatment; *E*, three months after treatment.

TABLE VII. Q-T INTERVAL IN V_5 BEFORE TREATMENT, AFTER SECOND INJECTION, AFTER TENTH INJECTION, AND TWO WEEKS AFTER TREATMENT

	BEFORE (SEC.)	AFTER SECOND INJECTION (SEC.)	AFTER THIRD INJECTION (SEC.)	TWO WEEKS AFTER TREATMENT (SEC)
Minimum	0.32	0.30	0.32	0.32
Maximum	0.38	0.40	0.44	0.38
Mean	0.348	0.351	0.358	0.356

SUMMARY

1. Electrocardiographic changes observed during Anthiomaline treatment of schistosomiasis were limited to the T waves and to the Q-T interval.

2. A decrease in amplitude of the T waves was present in 90 per cent of the cases. In the standard leads, the changes in the T waves were so slight that they could not, per se, be considered to be of pathologic significance. A negative T_1 was not encountered.

3. The changes in the T waves were more pronounced in the precordial leads. A boy, 12 years of age, showed negative T waves in Leads V_1, V_2, V_3, and V_4, following the tenth injection, when the control record showed negative T waves only in Leads V_1 and V_2; and a man, 24 years of age, who originally showed only a diphasic T wave in Lead V_3, showed negative T waves after the tenth injection in all six precordial leads.

4. With negligible or no changes in pulse rate, there was found a prolonged Q-T interval in about 50 per cent of the cases, more marked after the tenth injection in both standard and precordial leads.

5. It appears that the electrocardiographic changes which occur during Anthiomaline treatment of schistosomiasis are less pronounced than those observed during treatment with tartar emetic, and compare favorably with the changes induced by Fuadin.

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Clinical Reports

BACTERIAL ENDOCARDITIS

Report of a Case in Which a True Musical Diastolic Murmur Appeared and Disappeared

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A CASE report of a patient with acute bacterial endocarditis with postmortem examination is presented. It is deemed worthy of reporting for the following reasons: (1) With the use of the new antibiotics in the treatment of various forms of bacterial endocarditis, there has been renewed interest in these diseases. (2) A survey of English literature for the past twenty years reveals no case showing the appearance and disappearance of a true musical murmur. This case shows this, and there is available a satisfactory physiologic and pathologic explanation. (3) The effect that a mechanical heart defect plays in precipitating heart failure is re-emphasized and the improvement of heart failure which accompanies improvement in the valve defect is clearly shown.

CASE REPORT

The patient, a 61-year-old white man, was admitted to the hospital on Jan. 21, 1946. His chief complaints were anorexia and loss of weight. These symptoms had been present for approximately three months. Fatigue had been present from the onset of the present illness and breathlessness, for only a few days prior to hospital admission. On the morning of admission, slight swelling of the ankles was apparent.

The past history was one of good health, with no serious illnesses or accidents. There was no history of rheumatic fever or syphilis.

Physical Examination.—The temperature was 100.8° F.; pulse rate, 85; respirations, 20 per minute; and blood pressure, 170/80. The patient was a poorly nourished, but well-developed man, who was in no acute distress. A few moist râles were heard at the base of each lung. The heart was enlarged. There was a diastolic murmur heard best over the aortic area and along the left sternal border and a diastolic murmur at the apex, with a thrill, diastolic in time, at the aortic valve area. The liver was palpable 3.0 cm. below the right costal margin. There was a 1 plus pitting edema of both ankles. The prostate was moderately enlarged, firm, smooth, and nontender.

Laboratory studies on admission showed a urine with specific gravity of 1.013, 1 plus albumin, 65 to 75 white blood cells, and 2 to 4 red blood cells per high-power field, and rare hyaline casts.

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The blood showed 3,280,000 red blood cells, hemoglobin of 60 per cent, 12,100 white blood cells, 93 per cent polymorphonuclear leucocytes, 3 per cent lymphocytes, and 4 per cent monocytes. The nonprotein nitrogen was 60 mg. per cent. A blood culture taken on admission was reported to be positive for nonhemolytic streptococci after three days of culture.

One day after admission and several hours following a 500 c.c. transfusion of citrated blood, the patient developed severe pulmonary edema, for relief of which, the removal of 500 c.c. of blood was required. A high-pitched, loud, musical diastolic murmur was then noticed which could be heard at any point on the patient's chest (anterior or posterior), over the upper abdomen, and over the upper humerus. This was confirmed by stethogram (Fig. 1). He remained in severe cardiac failure and required digitalization, oxygen, aminophyllin, and morphine. At this time, the blood pressure changed gradually from 170/70 to 150 to 160/0 to 30 (Fig. 2), and the nonprotein nitrogen rose to 100 mg. per cent. Penicillin, 15,000 units every three hours, was started and increased to 40,000 units every two hours two days later.

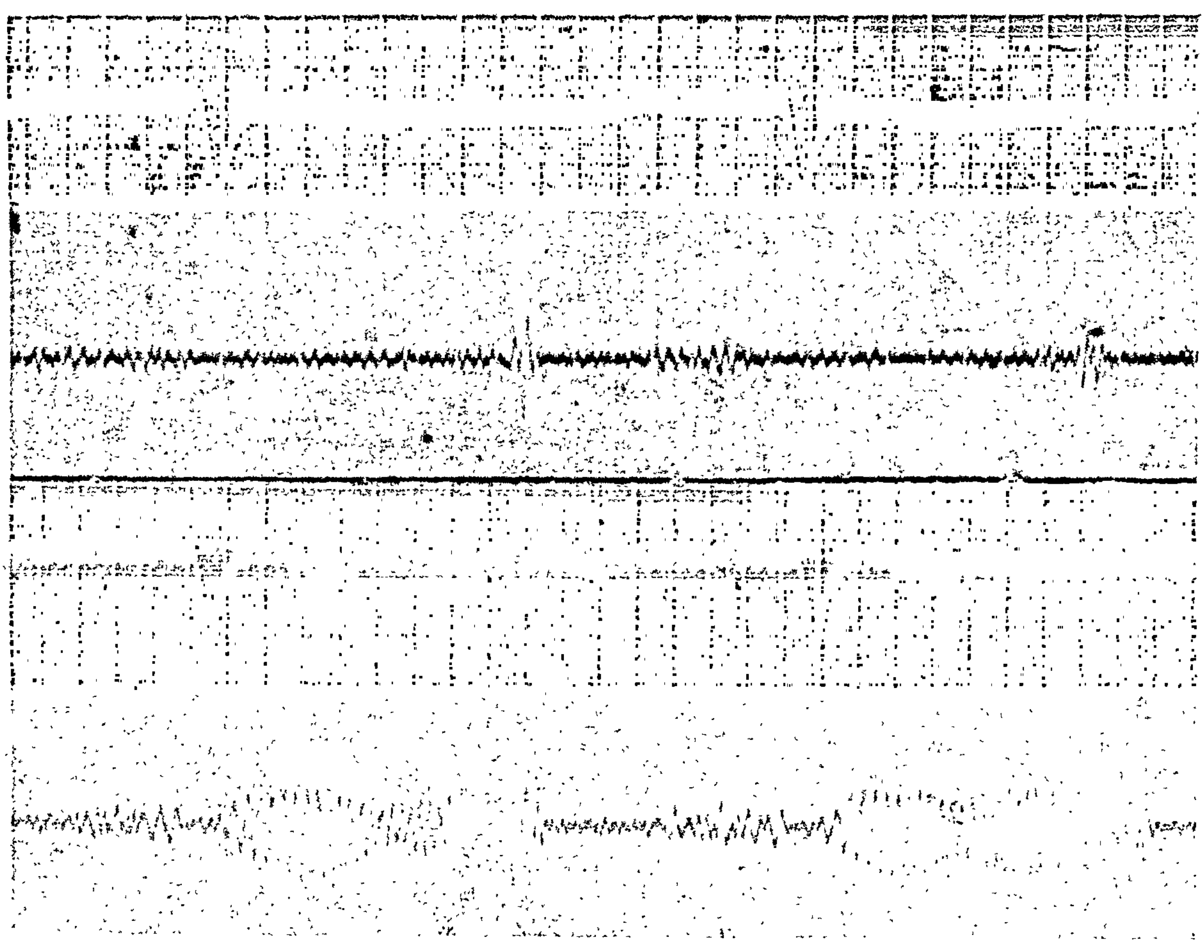

Fig. 1.—Stethoscopic electrocardiograms. Upper, musical murmur present, Jan. 25; lower, musical murmur absent, Feb. 21.

Failure was marked and continued. Severe dyspnea and orthopnea, distended neck veins, basal lung moisture, enlargement of the liver, and ankle edema were present. On Feb. 11, 1946, twenty days after admission, the high-pitched, musical murmur gradually disappeared; the change was confirmed by a stethogram (Fig. 1). The symptoms and phenomena of cardiac failure rapidly diminished. The nonprotein nitrogen was reduced to 30 mg. per cent from a previous level of 100 mg. per cent.

By February 19, the patient was able to be up in a wheel chair. The improvement was thought to be due to a healing of the aortic valve; however, positive blood cultures for the same organism, a gram-positive gamma streptococcus, were still obtained. The laboratory reported

the organism to be penicillin resistant, but inhibited by 5 units of penicillin per milliliter, so that the dosage was increased to 80,000 units every two hours.[3] The blood pressure no longer showed the wide pulse pressure but had gradually returned to 125/70 (Fig. 2). Sulfadiazine was started and penicillin continued, but in spite of this therapy, repeated blood cultures were reported to be positive for the same organism.

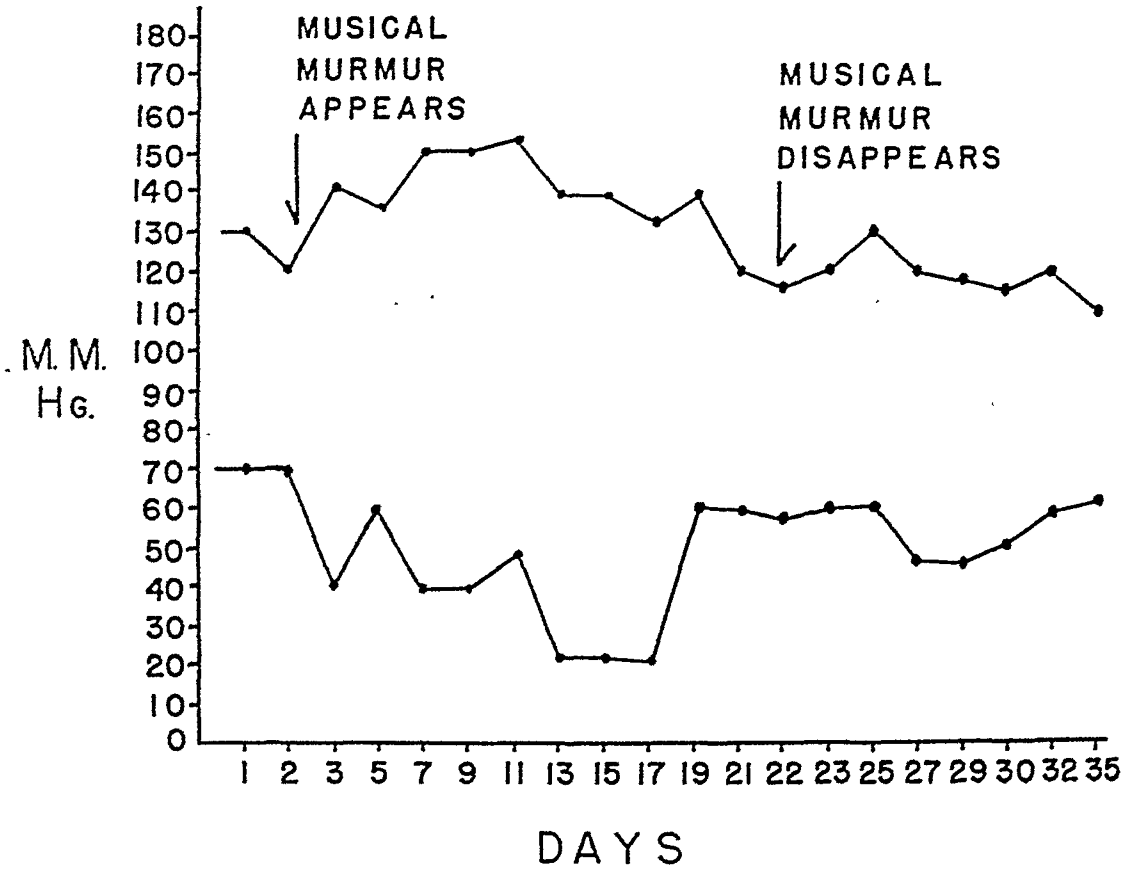

Fig. 2.—Blood pressure readings showing wide pulse pressure with musical murmur present.

On February 25, the patient's clinical condition was worse. There was a low-grade fever, 98 to 101.4° F., congestive failure had gradually but steadily increased, and there was a progressive downward course. Death occurred on April 2, 1946, seventy days after admission. Penicillin, 39,217,000 units, had been administered.

Post-Mortem Examination.—The findings pertaining to this report were in the heart. Elsewhere, the findings were: severe pulmonary congestion with edema, moderate chronic passive congestion of the liver, a solitary splenic abscess of metastatic origin (septic infarct), benign prostatic hypertrophy, and moderate atherosclerosis of the aorta. The kidneys were of normal size and sections showed patchy areas of fibrosis of glomeruli and destruction of tubules.

The heart was grossly enlarged, weighing 700 grams. The pericardium was normal. The myocardium was firm and thickened. The pulmonary and tricuspid valves were essentially normal. The leaflets of the aortic valve were involved in a bacterial process, with vegetations which averaged 5.0 mm. in their greatest diameter. They were firmly attached and nonfriable. The posterior and right cusps were perforated along the inferior margin, the perforations measuring 2.0 to 3.0 mm. in diameter (Fig. 3). Each perforation was blocked by a large bacterial vegetation which occluded the opening in the valve cusps produced by the perforation. The endocardium of the anterior leaflet of the mitral valve was involved by one large vegetation. The chordae

tendineae of this valve were shortened but not thickened. Neither valve showed gross pathologic evidence of previous scarring. The coronary ostia were patent and the arteries were functional throughout.

Microscopic study of the heart revealed edema of the endocardium around the aortic cusps. The vegatations of the aortic valve were shown to be composed of platelets, fibrin, polymorphonuclear leucocytes, and lymphocytes. Clusters of bacteria were seen on the outer surfaces and Gram's stain showed these to be gram-positive cocci.

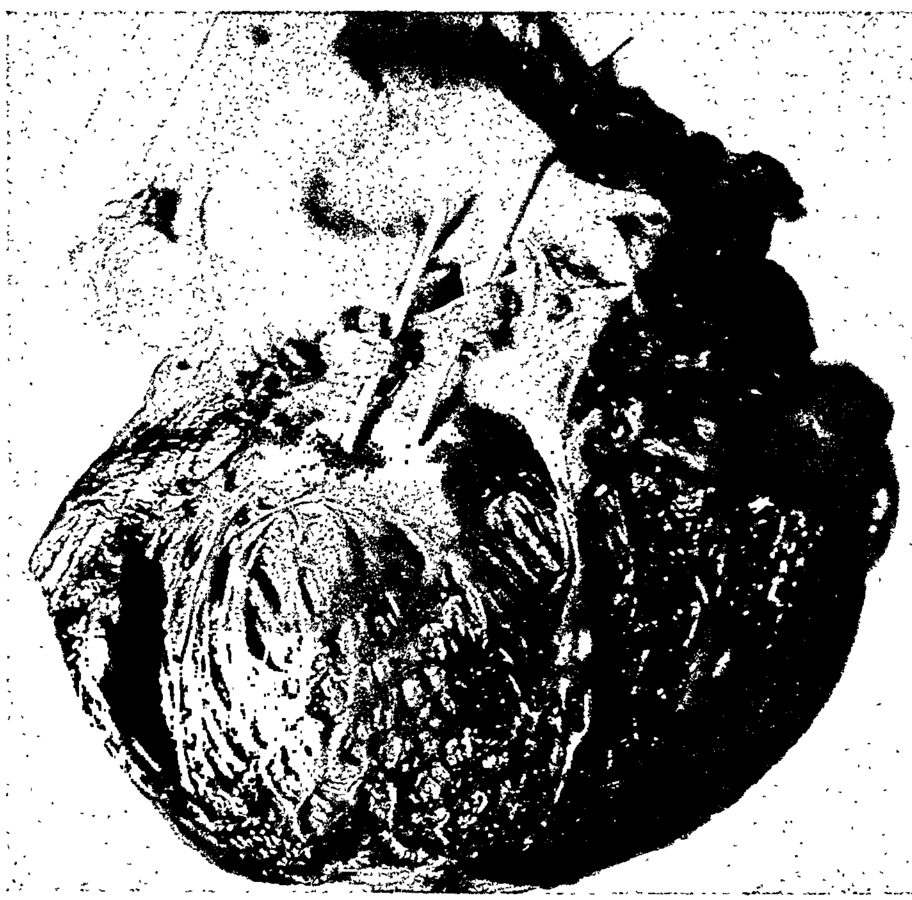

Fig. 3.—Photograph of heart showing perforations of aortic valve.

DISCUSSION

In the case which has been presented, symptoms were of approximately five and one-half months' duration. This prolonged course, with the marked improvement after the disappearance of the musical murmur, led us to believe that recovery was taking place. The repeatedly positive blood cultures and the subsequent course showed that this optimism was unjustified. Undoubtedly, the large dosage of penicillin, 39,217,000 units, inhibited the progression of the disease and allowed it to be of longer duration than usual.

The most interesting clinical observation was the appearance of the musical murmur, and, later, its disappearance, together with the effect that these changes had upon the clinical course. Cardiac function was fair until the development of the perforations of the leaflets of the aortic valve, which caused the murmur. Immediately after the perforation, the patient developed severe cardiac failure. The effect of sudden perforation of an aortic valve leaflet was previously ob-

served by Porter[4] in a case of gonococcal endocarditis in which the patient developed a musical murmur and perforation of the aortic valve while he was being examined. Our patient, fortunately, lived longer so that we were able to observe him at greater length. As long as the musical murmur was present, cardiac failure was irreversible, with the severity of failure being definitely related to the pulse pressure. With the disappearance of the musical quality of the diastolic murmur there was lessening of the pulse pressure and improvement, which was probably related to lessening of aortic insufficiency due to plugging of the perforations by vegetations.

SUMMARY

A case of acute bacterial endocarditis due to a gamma (nonhemolytic) streptococcus, in which death occurred in spite of massive penicillin therapy, has been reported. A true musical diastolic murmur, caused by perforation of two cusps of the aortic valve, occurred during the course of the disease. This was accompanied by severe congestive heart failure. With the disappearance of the musical quality of the aortic diastolic murmur, there was a prompt lessening of the pulse pressure and a progressive improvement in the symptoms and the degree of heart failure. What was interpreted as evidence of improvement was in reality increase in the size of vegetations on the aortic valve which produced occlusion of the perforations of the valve.

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CORONARY OCCLUSION WITH MYOCARDIAL INFARCTION FOLLOWING CHOLECYSTECTOMY FOR RELIEF OF ANGINAL PAIN IN A PATIENT WITH CHOLELITHIASIS

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THE inter-relationship between the pain caused by diseases of the coronary arteries and the biliary tract is well recognized. Miller[1] believes that this inter-relationship is due to a common autonomic reaction and that a common afferent pathway is brought into action when the referred pain of coronary artery disease simulates that of gallbladder and biliary duct disease, and vice versa.

In experimental distention of the human gallbladder, changes in heart rate, disturbances in rhythm, and changes of the T waves have been found.[2] Buchbinder[3] found that in icteric animals a reflex mechanism from distended biliary passages caused cardiac arrhythmias and heart block, probably by way of the vagus nerve. Further, Gilbert[4] has shown both experimentally and clinically that stimuli originating in the gallbladder or in the bile ducts may cause a decrease in the coronary blood flow, which results in a disproportion between blood supply and blood needs similar to those which occur when intrinsic anatomic changes take place in the coronary vessel wall. The belief has been expressed by Owen[5] that a heart which is already damaged by coronary sclerosis might, in the presence of disease of the biliary tract, show electrocardiographic abnormalities on much less provocation than would a normal heart. Patients with organic heart disease, particularly patients with angina pectoris, who were greatly benefitted by the removal of the diseased gallbladder, were reported by Babcock.[6,7] In addition, Hamburger and Strauss[8] described patients whose cardiac arrhythmias disappeared, and whose electrocardiograms became normal following cholecystectomy.

In the experience of Ravdin,[9] the risk incurred in operating upon such patients is not great provided they receive proper care before and during operation. A number of patients who had been unsuccessfully treated for severe anginal pain by competent internists became symptom free following cholecystectomy performed by Verdi.[10] White,[11] however, warns that cholecystectomy may occasionally be followed by coronary occlusion with myocardial infarction.

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In the case herein reported, this complication occurred, but remained unrecognized for twelve days.

CASE REPORT

H. P., a man, 49 years of age, was admitted to a general hospital in June, 1946, with a four-month history of substernal pain and slight dyspnea, brought on by heavy exercise. The substernal pain on exertion occurred from five to six times daily, but at times was absent for several days. It did not directly radiate but it was associated with severe pain in one or both elbows, and with dizziness. No perspiration or pallor was present during these attacks. The pain lasted from one to ten minutes if untreated, but responded promptly to nitroglycerin. The patient noticed that he became tired easily. He complained also of an abdominal fullness and slight epigastric pain, which he described as gas pain, following meals. There was no history of biliary colic, jaundice, or clay colored stools.

The past history was negative, except for influenza. The patient smoked thirty cigarettes daily and drank alcoholic beverages moderately and occasionally.

On physical examination, the patient did not appear to be acutely or chronically ill; he was slightly undernourished, and looked older than his stated age. No cyanosis was present. The ocular fundi showed no abnormalities. The blood pressure was 110/60; the pulse rate was 65 per minute and regular. His temperature was 98.4° Fahrenheit. Heart and lungs were normal to percussion and auscultation. The examination of the abdomen revealed no masses, tenderness, or rigidity. The pulse of the dorsalis pedis artery was easily palpable bilaterally.

The white blood count was 7,800 and the hemoglobin was 90 per cent. The differential count showed 60 per cent neutrophiles, 39 per cent lymphocytes, and 1 per cent monocytes. The Kahn test was negative. Examination of the urine revealed nothing significant. The clotting time was 1.5 minutes (capillary method).

Roentgenographic examination of the chest revealed normal heart and lungs, and no evidence of diaphragmatic hernia in the Trendelenburg position. Cholecystograms following administration of Priodax tablets showed normal gallbladder function but numerous small choleliths.

The resting electrocardiogram was within normal limits. An exercise tolerance test brought out signs of coronary insufficiency manifested by low T waves in Lead I and diphasic T waves in Lead CF_4, three minutes following exercise (Fig. 1).

In view of these findings, it was thought that the patient's cardiac complaints could be aggravated by the coexisting cholelithiasis. It seemed probable that cholecystectomy might improve the patient's cardiac status, despite the fact that the biliary symptoms were minimal. Consequently, cholecystectomy and appendectomy were performed on June 7, 1946. The patient was anesthetized with 9 c.c. of sodium pentothal and 4 ounces of ether. The operation required two hours, but no serious difficulties were encountered. Dense adhesions were found around the gallbladder, but the common duct was probed and found to be patent. The thickened gallbladder was 8.0 cm. long and 4.0 cm. wide and contained about 100 small, dark brown, irregular stones. The pathologic diagnosis was chronic cholecystitis with cholelithiasis, and normal appendix.

The postoperative course was reported by the surgical staff as uneventful. The patient was allowed to be out of bed on the first postoperative day. He resumed normal activity on the ninth postoperative day, and on the twelfth postoperative day he was discharged from the surgical service. On this day he walked about one-half mile without considerable discomfort. Although the patient had no immediate complaints except fatigue, an electrocardiogram showed signs of a recent anterior myocardial infarction (Fig. 2). A white blood count was 7,400. The corrected sedimentation time was 39 mm. in one hour. The clotting time was 2 minutes.

On more careful questioning, the patient acknowledged that on the first postoperative day he had experienced upper abdominal pain which was associated with pain in both elbows. The pain in the abdomen and left elbow lasted for the entire day, that in the right elbow, for three days. There was no pain in the shoulders or in the upper arms. Symptoms were not severe enough to require narcotics nor to confine the patient to bed.

As soon as the abnormal electrocardiogram was seen, the patient was placed on strict bed rest. The subsequent course was uneventful. Four months after the operation the patient felt well, and complained only of exertional dyspnea and occasional chest pain. Electrocardiograms taken at intervals showed persisting signs of anterior myocardial infarction.

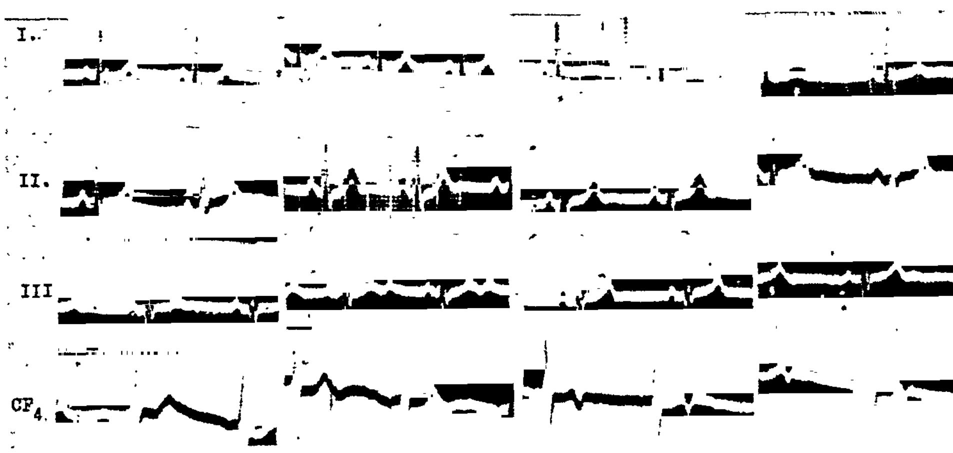

Fig. 1.—Exercise tolerance test shows signs of coronary insufficiency. The upright T_1 becomes almost isoelectric; the upright T of CF_4 becomes diphasic three minutes after exercise. *A*, Resting recumbent on June 2, five days prior to operation; *B*, immediately after exercise; *C*, three minutes after exercise; *D*, eight minutes after exericse.

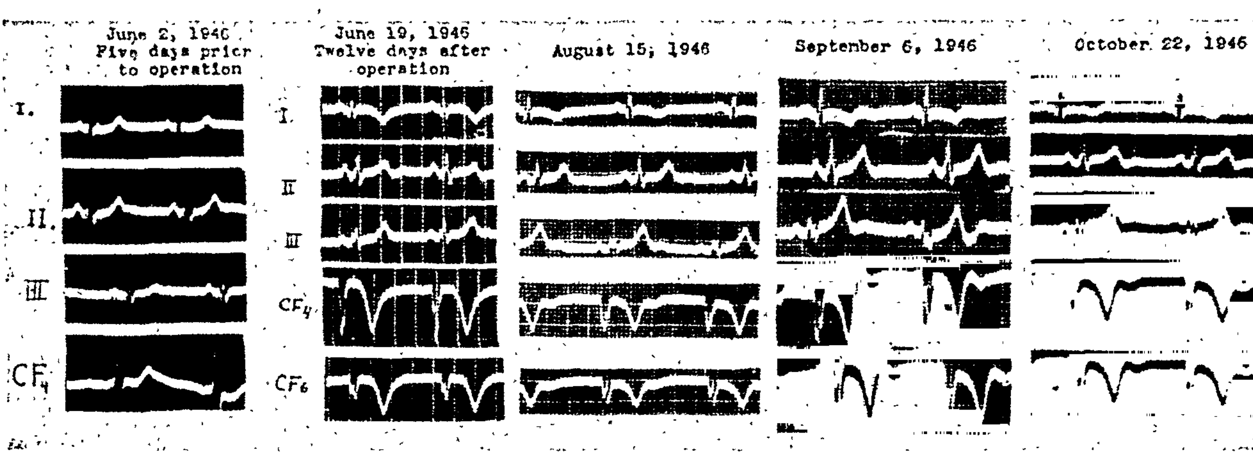

Fig. 2.—Electrocardiograms before and after cholecystectomy. The first electrocardiogram after operation was taken June 19, 1946, for a routine check-up. No myocardial infarct was suspected.

DISCUSSION

It is a matter of pure conjecture whether the myocardial infarction was precipitated by the trauma of the operation or whether it would have occurred without operation. It is of importance, however, that the symptoms of myocardial infarction were mistaken for wound pain and that the patient was allowed to leave his bed one day after the operation, the day on which myocardial infarction probably occurred. Considering the fact that, on one hand, the most valuable treatment of myocardial infarction is prolonged bed rest and

that, on the other hand, the trend of modern surgery is toward short periods of bed rest, a mistake of this kind could, theoretically at least, be of great consequence.

Routine postoperative electrocardiograms on every patient with known coronary artery disease prior to mobilization and on every patient in whom there is severe abdominal pain following operation could greatly reduce the danger of overlooking a myocardial infarct.

SUMMARY

1. A case of anterior myocardial infarction immediately following cholecystectomy and appendectomy in a patient with cholelithiasis and coronary artery disease is reported.

2. The primary purpose of the operation, in this case, was the relief of anginal pain by the removal of extracardiac causes of the pain.

3. The pain of myocardial infarction was mistaken for postoperative wound pain.

4. Routine postoperative electrocardiograms taken in such patients may prevent such errors.

The author gratefully acknowledges the advice of Dr. W. F. Verdi and Dr. H. M. Marvin in making this report.

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Abstracts and Reviews

Selected Abstracts

Siegmund, O. H., Nash, V. L., and Granger, H. R.: The Vasopressor Activity of Some New Orally Active Sympathomimetic Amines. J. Pharmacol. & Exper. Therap. **92:** 207 (March), 1948.

The vasopressor effects of a small group of orally active phenyl and cyclohexylisopropyl amines were investigated.

These compounds produced prolonged vasopressor effects comparable to amphetamine in unanesthetized and anesthetized dogs. The central nervous system stimulating effect could be diminished by saturation of the ring of several phenyl compounds to produce cyclohexyl compounds.

GODFREY.

Burch, G., and Ray, T.: Cardiovascular System as the Effector Organ in Psychosomatic Phenomena. J.A.M.A. 136:1011 (April 17), 1948.

Burch and Ray emphasize the extreme susceptibility of the cardiovascular system to psychic influences in both health and disease and cite literature illustrating the well-recognized central (cardiac) and peripheral (vascular) manifestations which result from emotional stimuli. The cardiac effects embrace increase in cardiac output, electrocardiographic changes, various arrhythmias, the precipitation of angina, and even sudden death. The peripheral effects consist of vasodilation and vasoconstriction with resultant changes in systemic blood pressure and in local temperature and color.

The authors point out that heretofore, the approach to the study of the cardiovascular reactions to emotional stimuli has rested largely upon clinical evaluation and observation, blood pressure determinations, electrocardiographic and thermometric studies, and measurements of cardiac output. Because of the accessibility and reactivity of the blood vessels of the digits, the authors feel that quantitative plethysmographic studies of these vessels afford another objective approach to the problem.

By means of a portable plethysmographic apparatus they recorded the changes of vascular volume of the tips of the index finger and/or second toe in a series of normal subjects and patients with known psychiatric difficulties, usually anxiety neurosis. Test stimuli of various types resulted in immediate and definite plethysmographic changes (reduction in the volume of pulse deflections, reduction in the total volume of the part, and alterations in the alpha deflections). The authors offer this objective method of study as another clinical means of exploring the psychosomatic cardiovascular reactions.

HANNO.

Smith, H. W.: Hypertension and Urologic Disease. Am. J. Med. 4:724 (May), 1948.

The author points out that it is not yet proved that human hypertension has its origin in either pathologic or functional disturbances of the renal circulation, despite all of the knowledge available from the Goldblatt experiment. An equally good interpretation of the data available is in terms of a generalized pathologic process which, by arteriolosclerosis and possibly other

mechanisms, attacks the renal parenchyma along with other organs. Sympathectomy lowers the blood pressure in some instances, but it has not yet been demonstrated that it changes the temporal progress of the disease.

The fallacies involved in dependence either on the blood pressure or the patient's symptoms as a guide in evaluating progress of the disease and the value of various therapeutic procedures is pointed out. Statistical data on blood pressure among the general population indicate that the incidence of essential hypertension is quite low before the age of 20 years, affects 25 per cent of the general population who have reached the age of forty years, and is present in 60 per cent of elderly persons.

The available evidence points to the fact that the incidence of hypertension is not increased by urologic disease and that the incidence of urologic disease is no greater among hypertensive than among normotensive subjects. Review of the literature on unilateral nephrectomy has revealed a cure of the hypertension in only forty-seven instances of 242 reported operations. The author concludes that the advisability of nephrectomy must rest upon conservative and recognized surgical indications and not upon the hope of reducing blood pressure.

WOODS.

Ostling, G.: The Significance of the Speed of Injection for the Therapeutic Effect of K-Strophanthin. Acta med. Scandinav. 129:77 (No. I), 1947.

Because of contradictory assertions in the literature regarding the advisability of slow as opposed to rapid injection of strophanthin, the author assessed the effect of daily one- to two-hour infusions of 0.5 mg. or less on twenty-three patients who had congestive failure with or without auricular fibrillation. Seventeen improved, with increased diuresis, loss of weight, and lowered heart rate. One died fourteen hours after a stenocardial attack which followed the infusion by an hour. The results were thought comparable to those obtained with faster injection, and there appeared to be no advantage in extending the time of injection beyond one minute. The author believes that the significance of the speed of injection of strophanthin has been overstressed.

SAYEN.

Mainzer, F.: Electrocardiographic Study of Typhoid Myocarditis. Brit. Heart J. 9:145 (Oct.), 1947.

The electrocardiographic findings in 254 tracings from 106 patients are reported. A few had paratyphoid infections. Thirty-nine had one tracing during convalescence; sixty had from three to seven tracings during and after the febrile state; seven were treated with chinine-bismuth-iodide and had one tracing during convalescence. Sixty of the 106 patients had abnormal tracings. The changes consisted of flattened, absent, or negative T waves, depressed or elevated S-T segments, low voltage with slurring or notching of the ventricular complexes, axis deviation to the right or left, and occasionally the appearance of Q waves. These changes occurred both with tachycardia and with bradycardia. A prolonged P-R interval was seen only once. The changes were twice as common in the febrile state as in convalescence. The changes persisted for from one to three weeks. Exertional tachycardia was present for weeks. It was uncertain whether the changes in the patients treated with chinine-bismuth-iodide were due to the disease or to the treatment.

The abnormal tracing is regarded as an expression of typhoid myocarditis. Clinically, typhoid myocarditis is manifested commonly by "forward failure" and in severe cases, by both "forward" and "backward" failure.

SOLOFF.

Segers, M., Vastesaeger, M., and Denolin, H.: Intraventricular Conduction Defects. Acta Cardiol. 2:166, 1947.

The classical electrocardiographic pattern of bundle branch block may be augmented by at least three additional types of intraventricular conduction disturbances:

1. Incomplete bundle branch block. This type is demonstrated in one example with incomplete left bundle branch block where late activation of the left ventricular surface and slurring

in the vectorcardiogram was present without reversal in rotation of the vector which is commonly noted in true bundle branch block. The slurring of the QRS complexes in standard limb leads in such instances is usually confined to the rising portion of QRS.

2. Focal intraventricular block. In this type, slurring of QRS is confined to the descending limb of QRS and is seen in the final portion of the ventricular loop of the vectorcardiogram. The pattern may represent lesions of the terminal branches of the conduction system.

3. Complex (bilateral) intraventricular block. In classical bundle branch block spontaneous changes in the form of the QRS complexes may occur and these may signal additional regions of impaired conduction. This is demonstrated in an example of left bundle branch block where the configuration of the standard limb leads changed spontaneously. Left bundle branch block was always present but special right-side chest leads revealed that during the period of change an additional conduction delay appeared over regions of the right ventricle. It confirmed the assumption that left bundle branch block was present with a focal lesion over the right ventricle.

HECHT.

Morelli, A., and Salvi, P.: Treatment of Essential Hypertension With Vitamin K. Progr. Med. (Naples) 3:611, 1947.

The authors studied the action of synthetic vitamin K as a possible hypotensive drug. In ten cases of essential hypertension, intravenous vitamin K was given in dose of 10 mg., and blood pressure variations and serum cholinesterase were studied. A transitory drop in blood pressure was observed which reached a maximum value within thirty minutes; this was followed by a gradual rise to the previous level. A parallel drop in the value of the serum cholinesterase was observed.

The mechanism of action of the drug is believed to be an increase in the parasympathetic tonus resulting from a decreased destruction of acetylcholine by the cholesterase.

LUISADA.

Vincent, D.: The Effect of Certain Cardiac Glucosides on Serum Cholinesterase. Compt. rend. Soc. de biol. 141:843 (Aug.), 1947.

Danielopolu's assumption that the action of digitalis compounds may be explained as primary inhibition of cholinesterase was tested in vitro by titrating horse serum containing various amounts of digitoxin, lanatoside C, ouabain, and scillaren against a solution of acetylcholine. No appreciable cholinesterase inhibition was observed. The cholinesterase activity of the serum of guinea pigs injected with digitoxin, ouabain, or lanatoside C (2 mg. per kilogram) was not appreciably altered when the samples were obtained prior to death from digitalis intoxication.

HECHT.

Bregante, L. J.: The Augmentation of the Effects of Vagal Stimulation Upon the Auricular Muscle of the Turtle by Veratrine and Sulfocyanate. Compt. rend. Soc. de biol. 141:846 (Aug.), 1947.

The negative chronotropic effect of vagal excitation (faradic stimulation) is augmented by veratrine sulfate in concentration of 1:100,000 to 1:200,000 and by sodium sulfocyanate in concentration of 1:10,000 to 1:20,000. It is assumed that the two substances lower the cardiac threshold to the inhibitory effects of potassium ions which may play a part in the cardiac response to vagal stimulation.

HECHT.

Migliaro, E.: Hypersensitivity of Cardiac Muscle to Potassium Ion Following the Administration of Veratrine and Sulfocyanate After Complete Atropinization. Compt. rend. Soc. de biol. 141:847 (Aug.), 1947.

Isolated heart preparations of frog and turtle suspended in Ringer's solution containing large amount of potassium revealed a striking sensitivity to the inotrophic action of potassium following the administration of veratrine and sulfocyanates even after atropine had been added in sufficient quantities to the perfusion fluid. The decrease in amplitude of myocardial contraction when the

preparation is in Ringer's solution containing three times the amount of potassium ranges from 20 to 50 per cent. Following administration of the two compounds the decrease amounts to 75 to 100 per cent of the normal amplitude. HECHT.

Binet, L., and Burstein, M.: The Reaction of the Peripheral Vascular System of the Dog to Stimulation of the Central End of the Vagus Nerve. Compt. rend. Soc. de biol. 141:971 (Oct.), 1947.

Faradic stimulation of the central end of a completely vagotomized animal results in marked rise in arterial blood pressure. When the circulation of the paw of these animals is measured by canulation and perfusion with homologous blood it can be demonstrated that weak faradic stimulation results in increased flow through the extremity while strong stimulation results in a sharp decrease. It is argued that strong faradic stimulation enhances the secretion of humoral substances, presumably epinephrine, and that such endocrine factors contribute to the response obtained. It is stated that in cross circulation experiments blood obtained during strong faradic stimulation is capable of producing vasoconstriction when perfused throughout the extremity of a nonstimulated animal. HECHT.

Padilla, T., Cossio, P., Berreta, J. A., and Alvarez, G. H.: Sympathectomy in Essential Hypertension. Medicina 7:429 (Oct.), 1947.

Twenty-nine patients were subjected to postganglionic and bilateral supra- and infradiaphragmatic splanchnic resection (Smithwick), and five, to an infradiaphragmatic resection alone (Adson). Eleven of these patients presented evidence of severe retinal involvement (Grade III and IV), but none had appreciable renal impairment. The early results were encouraging, but after a period of two years, less than 20 per cent were benefited by the operation. The procedure is not recommended as a treatment for the hypertensive syndrome, even in selected cases. The operative mortality was 10 per cent. HECHT.

Chardon, G., Gross, A., and Fourrier, A.: On the Cause of Cardiac Acceleration During Anoxia. Compt. rend. Soc. de biol. 141:1050 (Oct.), 1947.

The increase in heart rate following inhalation of a mixture containing 10 per cent oxygen appears to be the result of stimulation of the carotid sinus. In the denervated animal, no alteration in heart rate is observed. It is suggested that during induced hypoxia epinephrine is excessively secreted. In addition to the possible effects of low oxygen tension on the central nervous system as the cause for tachycardia, a temporary hyperadrenalinemia is implicated.

HECHT.

Charlier, R., and Philippot, E.: Heart and Carotid Sinus. II. Endo-sinusal Hypotension and Right Ventricular Pressure. III. Endo-sinusal Hypotension and Cardiac Dynamics in the Sympathectomized and in the Completely Denervated Heart of Dogs. Arch. internat. de pharmacodyn. et de thérap. 75:135 (Nov.), 1947.

In nine anesthetized dogs occlusion of the carotid sinus resulted in a prompt increase in right ventricular pressure obtained by cardiac catheterization. The cardiac output increased from 20 to 70 per cent. During the experiment an increase in oxygen consumption and in pulmonary ventilation occurred and the arteriovenous oxygen difference decreased. As the arterial pressure rose considerably, cardiac work increased from 50 to 120 per cent. Intra-auricular pressures, however, remained relatively unchanged. A sharp fall in right ventricular pressure and in cardiac output, independent of changes in arterial pressure, was noted in two instances following section of the vagus nerve. The response of the cardiovascular system to occlusion of the carotid sinus, and particularly the rise in cardiac output, decrease in arteriovenous oxygen difference with high oxygen values for the mixed venous blood, and the rise in arterial pressure, occurred even when sympathetic and parasympathetic fibers to the heart were sectioned. The pressure response following occlusion of the sinus must, in part, be explained by a reflexly increased cardiac output.

HECHT.

Fauteux, M.: Cardiac Resuscitation. J. Thoracic Surg. **16**:623 (Dec.), 1947.

The author defines cardiac resuscitation as "full and durable restoration, in due time to avoid eventual death, of the essential functions of a heart which has lost its power to propel blood, and which, in all appearance, is unable to recover its effective value as a pump." He then points out that restoration in the strict sense is rare, clinically and experimentally, following cardiac standstill and ventricular fibrillation.

As a result of an extensive experience with experimental studies of resuscitation of the heart from cardiac standstill and ventricular fibrillation, the author believes that the following drugs, employed properly, are of value: (1) Procaine, 1.0 or 2.0 c.c. of a 2 per cent solution, injected slowly into the right or left auricle, has a significant effect on the irritability of the heart, decreasing it greatly. Injection of the procaine into the blood stream is more effective than topical application to the epicardium. (2) Barium chloride, 1.0 to 2.0 c.c. of a 0.5 per cent solution, is effective in increasing the force of the heart beat, and also in increasing cardiac tone. Overdosage causes death in systole. The drug can be administered also by injection directly into the auricle. (3) Epinephrine, 0.5 to 1.0 c.c. of a 1:1,000 solution (0.1 per cent), is of value in increasing the rate and strength cf the heart, but in some instances can initiate ventricular fibrillation.

Certain physical factors are also useful in cardiac resuscitation: (1) Cooling of the overheated heart resulting from repeated electrical shocks is of value. (2) Cardiac massage is immensely important in restoring coordinated beats to the heart which is in standstill. (3) Electrical shocks are of value in defibrillating the heart which is in ventricular fibrillation. (4) Intracardiac transfusion may aid in overcoming peripheral circulatory failure.

Fauteux points out that the essential accidents which must be prevented during an elective operation on the heart are: (1) hemorrhage, (2) serious circulatory disturbances due to unwise manipulations, (4) reflexes of various nature, (5) cardiac standstill, and (5) ventricular fibrillation. All of these accidents can be managed by present-day knowledge but are dependent on the surgeon's experience with animal experiments, on an adequate armamentarium in the operating room, and finally, on the electrocardiogram as a constant recorder of the effects of manipulation on the rhythm of the heart. LCRD.

Harken, D. E.: The Removal of Foreign Bodies From the Pericardium and Heart: A Moving Picture Demonstration. J. Thoracic Surg. **16**:701 (Dec.), 1947.

The author employed motion pictures to demonstrate three operations illustrating important points in the removal of foreign bodies from the heart and the pericardium. There were 134 missiles removed from the mediastinum in his experience in England. Fifty-five were pericardial and thirteen were in the chambers of the heart. Seventeen cardiotomies were performed and there were no deaths.

It was felt that the following four indications should determine whether foreign bodies should be removed from the heart: (1) to prevent embolus of the foreign body or associated thrombus; (2) to reduce the danger of bacterial endocarditis; (3) to avoid recurrent pericardial effusions; and (4) to reduce damage to the myocardium. It should be added, however, that in their experience, the number of foreign bodies which were not operated upon was greater than those which were removed. The ones not operated upon produced, of course, no symptoms.

The operation demonstrated in the first motion picture revealed an abscess in the pericardial sac in which 18 c.c. of purulent material was present around the foreign body. On culture the organism grown was *Clostridium welchii*. Dislocation of the heart during the maneuver produced significant changes in the electrocardiogram which was being made at the time of the operation. These changes included right bundle branch block. At the completion of the manipulation of the heart, normal rhythm was restored. The patient made an uneventful recovery. The author feels that bathing the heart with Novocain (1 per cent) is important in preventing abnormalities of rhythm; the drug also has a potentially specific depressor action on the heart.

The second motion picture showed an operation for the removal of a missile from the right ventricle. There was a zone of damage to the overlying myocardium. By means of two staggered rows of hemostatic U sutures of number zero chromic catgut, hemostasis was maintained while the heart muscle was incised and the foreign body removed by the grasping forceps. Four trans-

fusions of 1,000 c.c. of fresh whole blood were used to replace the estimated loss of 800 c.c. of blood during this manipulation. The patient withstood the procedure well and hemostasis was adequate after the sutures were tied and a free patch graft of pericardium was tacked over the incision into the myocardium. It was also felt important to leave a decompression window several centimeters in diameter in the pericardium so that fluid could escape into the left pleural space. The chest wall was carefully reconstructed without drainage. This patient also made an uneventful recovery.

The third operation showed a patient who had been operated upon twice before in an attempt to remove a foreign body which lay in the right ventricle. The illustrated operation demonstrated that the removal was accomplished successfully and it also demonstrated that the previous cardiotomy site had healed satisfactorily. LORD.

Biorck, G., Gohle, O., and Westman, C.: Partial A-V Block and Duodenal Ulcer. Acta med. Scandinav. **130**:167 (No. 2), 1948.

Two male subjects, 14 and 26 years of age, both with duodenal ulcer and disturbed auriculoventricular conduction, are reported upon. One had orthostatic tachycardia which could be abolished by ergotamine, which, however, threw the patient from heart block of minor grade into a 2:1 or 3:1 block. Atropine would shorten the P-R interval. The older patient's auriculoventricular conduction time was 0.27 to 0.28 second in recumbency and became normal on standing.

The authors discuss the possibility of both ulcers and auriculoventricular conduction disturbances having a common mechanism consisting of increased vagal tone or some disturbance of the parasympathetic cerebral centers. A cardiologic survey is recommended for children and young adults who develop peptic ulcer as an aid in deciding whether the cause is local or whether the ulcer is one manifestation of a systemic disease. SAYEN.

Elmquist, A., and Rydin, H.: The Influence of Muscular Exercise on the Tolerance of Digitalis in Guinea-Pigs. Acta physiol. Scandinav. **15**:63 (No. 1), 1948.

Investigating the proposition that cardiac patients require more digitalis with increased physical exertion, the authors administered Digitotal subcutaneously for one month to two groups of guinea pigs. One group was forced to exercise for periods up to one hour after each injection. A third group served as controls. At the end of the experiment the minimal lethal dose of Digitotal was determined for all survivors by an intravenous injection.

The exercised guinea pigs were able to tolerate more digitalis than those not exercised, and the minimal lethal dose of the latter was smaller. The exercised guinea pigs required a minimal lethal dose comparable to that of the controls. These differences were analyzed statistically and proved significant. Muscular exercise is thus thought to increase the guinea pig's tolerance to digitalis; continuance of the investigation on clinical material is suggested. SAYEN.

Broden, B., Hanson, H. E., and Karnell, J.: Thoracic Aortography, Preliminary Report. Acta radiol. **29**:181 (No. 2), 1948.

The results of studying three patients by Diodrast aortography after a technique devised by Radner (Acta Radiol. **29**:178, 1948) are reported. A cardiac catheter (No. 7 to 9) was passed up the radial artery after this vessel had been exposed in the upper third of the forearm and a small transverse incision made in it between two clamps. The catheter could then be passed into the ascending aorta, the right radial artery directing it more satisfactorily than the left. The abdominal aorta and the opposite arm were compressed in order to delay transport of the 70 per cent Diodrast solution from the thoracic aorta. Fifty c.c. were injected as rapidly as possible. The resistance was very high and an average of seven seconds was required for each injection. Local anesthesia and light sedation were used. X-ray films were made simultaneously in two planes at a rate of one film per second. The aorta was well visualized in all three patients. Two of this number showed a coarctation. The radial artery was sutured satisfactorily in two of the patients and ligated without incident in the other. One patient developed considerable vasospasm during passage of the catheter.

The authors recommend their modification of Radner's method for the study of all aortic lesions but especially coarctation and atypical patent ductus arteriosus. They are attempting to devise a mechanical device to achieve a more rapid injection. SAYEN.

Fabricius, B.: Kymographic Studies of the Function of the Auricle. Acta radiol. 29:152, 1948.

Previous views as to the type of contraction of the auricular appendage are discussed and a study reported of the relation of left auricular appendage waves to the movements of the right atrial and the left ventricular border based on thirty-eight combined roentgen-kymographic and electrocardiographic recordings in twenty-two subjects. The movement of the auricular appendage was quite variable, no regular correlation with the motion of the rest of the heart being obtained. The author agrees with the observations on mammalian hearts made by Rollhäuser (Morphol. Jahrbuch 88:249, 1943) that the auricular appendage has no propulsive function but serves as a complementary space during ventricular systole to keep the surface of the heart constant, thus serving as an elastic filling material for the deep niches at the base in systole. When aneurysm of the pulmonic artery or of the ascending aorta fills the niches the auricular appendages have been found greatly decreased in size. SAYEN.

Clerc, A., and Quincaud, A.: Identical Electrocardiograms With Cardiac Apex Formed by Right or Left Ventricular Myocardium. Compt. rend. Soc. de biol. 142:151, (Feb.), 1948.

After ligatures were applied to both venae cavae and the azygos vein, the beating dog's heart was sectioned so that it was divided in two parts; one, the base of the heart with the great vessels attached, the other the apex of the left ventricle and the anterior aspect of the right ventricle. Lead II was recorded with the fragments in their normal relation, and then with apical fragment arranged so that the right ventricular myocardium formed the apex. Lead II appeared the same under both conditions. This led the authors to conclude that the form of the electrocardiogram is determined by the position of the heart and that it is the heart as a whole which determines the electrical axis. SEGALL.

Franck, C., Grandpierre, R., and Royer, P.: Transitory Apnoea in Man Induced by Breathing a Mixture Rich in Oxygen During a State of Anoxaemia. Compt. rend. Soc. de biol. 142:376 (March), 1948.

Human subjects were first rendered anoxemic by breathing pure nitrogen during one to four minutes; the gas was then changed to ordinary air or pure oxygen. This sudden change resulted in transitory apnea which tended to be longer the richer the oxygen content of this mixture. On the other hand, restoration of normal breathing is more regular and progressive with the richer than with the poorer oxygen mixtures. SEGALL.

Charlier, R.: The Role of the Carotid Sinus and the Cardio-Aortic Region in Reflex Regulation of Cardiac Output. Acta Cardiol. 3:1 (Jan.), 1948.

This paper presents in greater detail the findings reported in another communication (Arch. internat. pharmacodyn. et de thérap. 75:135, 1947). Clamping off both common carotid arteries results in a striking increase in cardiac output induced by an increase in venous inflow. This may come about by venous constriction and/or by the opening of possible arteriovenous channels (decrease in arteriovenous oxygen difference) or by both. It is assumed that the greater part of the increase in arterial blood pressure following the clamping of the carotid arteries or section of the four depressor nerves is the result of alteration in stroke volume. The conclusions are at variance with those reported by Heymans and his collaborators. HECHT.

Lequine, J., Denolin, H., and Verniory, A.: Dextrocardia and Septal Defects. Acta Cardiol. 3:56 (Jan.), 1948.

Two examples of dextrocardia both complicated by intraventricular septal defects are presented. The first resembled a tetralogy of Fallot, the second an Eisenmenger complex. From the

oxygen consumption and from arterial and (peripheral) venous oxygen content, the cardiac output, pulmonary circulation, and flow of blood through abnormal shunts were determined according to formulas by Van Slyke and by Bing. In the first case the venoarterial shunt was estimated as 15 per cent (0.38 liter), in the second as 50 per cent of the cardiac output (1.21 liters).

HECHT.

Cooper, F. W., Jr., Harris, M. H., and Kahn, J. W.: Ligation and Division of the Abdominal Aorta for Metallic Embolus From the Heart. Ann. Surg. 127:1 (Jan.), 1948.

The authors present a case report in which excision of the bifurcation of the aorta was necessitated by erosion of a portion of the vessel by a foreign body within its lumen. The patient had sustained a penetrating gunshot wound of the left arm and chest, and subsequently x-ray examination revealed a 45 caliber bullet at the bifurcation of the aorta. The missile was removed surgically from the vessel, and the aorta was ligated below the origin of the inferior mesenteric artery. An uneventful recovery occurred with a gradual increase in the circulation of the lower extremities.

It was the opinion of the authors that the good therapeutic result was due to the fact that the occlusion of the aorta, initiated by the foreign body, occurred over a period of several weeks, and that consequently an adequate collateral circulation had developed in the interval. Since the skin temperature of the toes actually increased after operation, it was felt that the procedure had removed a source of irritation of the arterial wall and hence eliminated the reflex vasoconstriction which results from such a condition.

ABRAMSON.

Segre, G.: On the Mechanism of Digitalis Action. Arch. internat. de pharmacodyn. et de thérap. 75:227 (Jan.), 1948.

The glucose metabolism of intact and hemolyzed horse erythrocytes is influenced by digitalis and by strophanthin in pharmacologically active concentrations. A decrease in glucose uptake is noted together with an increase in oxidation of lactic acid. The action is unimpaired and oxidation to lactic acid occurs in the presence of carbon monoxide and of cyanide. It is argued that the digitalis bodies act like a coenzyme and that they participate in glucose metabolism in the absence of coenzymase. It is assumed that these compounds may act as hydrogen carriers in an oxidation-reduction system.

HECHT.

Farah, A., and Maresh, G.: Determination of the Therapeutic Irregularity and Lethal Doses of Cardiac Glycosides in the Heart-Lung Preparation of the Dog. J. Pharmacol. & Exper. Therap. 92:32 (Jan.), 1948.

The authors found that on a molar basis the cardiac glycosides have the following order of decreasing potency: g-strophanthin, digoxin, digitoxin, oleandrin, and lanatoside B. The average ratios of irregularity dose to therapeutic dose, and lethal to therapeutic dose were the same for all five glycosides studied. These findings differ from other reports in which other methods and preparations were used.

GODFREY.

Gruber, C. M., and Keyser, G. F.: The Effects of Analgesic Drugs Upon Excised Frog and Terrapin Cardiac Vagus Nerve. J. Pharmacol. & Exper. Therap. 92:59 (Jan.), 1948.

Racemates A and B of 1-amino-1-phthalidylpropane hydrochloride, aminopyrine, antipyrine, and acetanilid were studied. The cardiac rate and contraction were measured. Racemates A and B when applied to the perfused frog heart decreased cardiac contraction and rate. The results with aminopyrine and antipyrine were variable. All drugs studied decreased the response of the heart to stimulation of the cardiac vagus nerve (terrapin). Racemate A was found to be twice as toxic to the heart as Racemate B.

GODFREY.

Farah, A., and Maresh, G.: The Influence of Sulfhydryl Compounds on Diuresis and Renal and Cardiac Circulatory Changes Caused by Mersalyl. J. Pharmacol. & Exper. Therap. 92:73 (Jan.), 1948.

In a well-controlled series of experiments in which both anesthetized and unanesthetized animals of two species (rabbit and dog) were used, the authors demonstrated that the diuresis

caused by mersalyl was abruptly and completely inhibited by 2, 3-dimercaptopropanol (BAL). The diuresis caused by intravenous infusion with sodium chloride and aminophylline was not inhibited by BAL. Cysteine hydrochloride and glutathione had no effect upon the diuresis of mersalyl even when given in very large doses. BAL, cysteine hydrochloride, and glutathione have all been found to be effective in inhibiting the cardiotoxic effects of mercurials.

To correlate the cardiotoxic inhibiting effects with the renal effects of BAL, cysteine hydrochloride, and glutathione, animals were given infusions of mersalyl and simultaneous records were made of blood pressure, electrocardiogram, and urinary output. When cardiotoxic manifestations occurred the sulfhydryl compound was given intravenously. BAL was found to inhibit both the cardiotoxic effects and the diuretic effect of the mercurial. Cysteine hydrochloride and glutathione inhibited only the cardiotoxic action.

The characteristic diuresis caused by mersalyl is initiated by a transient reduction in urinary output. This was shown to be due to a reduction in kidney blood flow. This reduction in blood flow is completely abolished by all three of the sulfhydryl compounds (BAL, cysteine hydrochloride, and glutathione). Since only BAL inhibits the diuresis, the evidence suggests that mercurials affect more than one process in the renal excretatory process. GODFREY.

Leriche, R., and Morel, A.: The Syndrome of Thrombotic Obliteration of the Aortic Bifurcation. Ann. Surg. 127:193 (Feb.), 1948.

The authors describe a syndrome related to a slow thrombotic obliteration of the terminal portion of the abdominal aorta. Patients with this condition are generally young men, who complain of an inability to maintain an erection and, eventually, permanent sexual impotency, extreme fatigue of both lower extremities, atrophy of these limbs, pallor of the legs and feet, even when standing, but no trophic changes either of the skin or of the nails. Examination reveals an absence of all pulses in the lower extremities and no oscillometric readings, even at the thigh, with a slight thrill present near Poupart's ligament. Pulsations can be felt in the aorta only above the level of the umbilicus. Although aortography will help to support the diagnosis, it should not be used in the presence of a reduced cardiac output or when the legs show cyanosis, since in such instances it may lead to the extension of the thrombosis with a fatal outcome. The fatigue in the legs is not the typical intermittent claudication but an extreme weariness which appears soon after the onset of walking and sometimes during standing. The pallor of the skin is quite striking, and this becomes even more marked when the limbs are elevated.

The pathologic change observed either at operation or post-mortem examination consists of a thrombotic process, generally beginning in one of the common iliac arteries and extending upward into the aorta. This hampers the blood flow to the opposite side but does not stop it entirely for some time. Ultimately the result is the obliteration of both iliac arteries and the aortic bifurcation. Less frequently the process first begins in the aorta and secondarily extends down into the iliac arteries. Generally there is an intensive periarteritis which attaches the thrombotic segment of the aorta to the surrounding tissues.

Aortic thrombosis may last for as long as five to ten years but eventually gangrene occurs. This is not sudden and is not always bilateral. It is preceded by an increasing muscular atrophy of the legs and thighs and an increasing impairment in walking. The acute terminal stage is ushered in by the appearance of edema and the development of a general violacious hue to the legs, with ecchymosis followed by ulcers on all pressure points; finally gangrene occurs. The lesions progress slowly. The prolonged survival can be explained by the extensive collateral anastomosis that is formed as the main channels slowly become thrombosed. The onset of the terminal period is probably due to upward and downward extension of the thrombosis.

According to the authors, the only treatment which has produced satisfactory results is resection of the thrombosed portion of the aorta and the obliterated iliac arteries, together with bilateral upper lumbar ganglionectomy. It is their belief that by removal of the thrombosed segments a source of vasoconstrictor reflexes is eliminated and, furthermore, the spreading thrombosis is checked.

ABRAMSON.

Kaldeck, R.: Transient Hemiplegia Following Electroconvulsive Treatment. Arch. Neurol. & Psychiat. 59:229 (Feb.), 1948.

The author presents a case of transient hemiplegia of several days' duration which developed following electroconvulsive treatment in a physically normal young woman with a schizoaffective psychosis. Electroshock treatment was given at weekly intervals. Two days after her tenth electroshock treatment she was unable to get up from bed. Neurological examination two days later showed that she was conscious and in fairly good contact, but tense and at times unwilling to cooperate. Her left arm and hand were limp and totally paralyzed; her left leg was weak and partially paralyzed. There were definite Hoffmann and Oppenheim signs on the left; the Babinski sign was equivocal. Two days later she showed pronounced improvement in the motor power of the left leg but was still unable to move the arm; slight movements of the hand were possible. On each of the following days the condition continued to improve. A year after the incident a neurological examination revealed nothing abnormal. A few weeks after termination of the shock treatment she relapsed into her previous mental condition. The experience of her hemiplegia has now been included in her paranoid ideation, and she refuses to submit to further electric treatment. Finally an electroencephalogram was obtained which proved to be normal.

The transient hemiplegia in this case is explained by the author on the basis of a vascular spasm. The arteriolar constriction must have lasted long enough to cause structural damage.

BELLET.

Gruhzit, O. M., Fisken, R. A., and Cooper, B. J.: Tetraethylammonium Chloride. Acute and Chronic Toxicity in Experimental Animals. J. Pharmacol. & Exper. Therap. 92:103 (Feb.), 1948.

Tetra-ethyl-ammonium chloride was administered both orally and parenterally to albino mice, albino rats, and dogs. With large doses, no matter what the route of administration, the animals died of respiratory failure within ten to thirty minutes. The following signs occurred before death: "Severe incoordination, flaccid prostration, respiratory and cardiac depression, marked ptosis and edema of eyelids, mydriasis, ocular muscle paralysis (inversion of eyeballs), erythema of ocular, nasal, and less so of buccal membranes, paralysis of accessory respiratory muscles of chest, and death from respiratory and circulatory collapse." Sublethal doses were well tolerated when given over long periods of time, even when the amount of drug given was large enough to cause some of these signs for two to three hours after administration. During chronic toxicity experiments with sublethal doses there were no hematologic, renal, or hepatic signs of damage that could be detected by blood counts, total blood nonprotein nitrogen, albumin-globulin fractions, bromsulfalein blood concentration, and urin analysis.

Necropsy lesions in acute toxicity experiments consisted in "severe congestive blood stasis and petechial hemorrhages in visceral organs, liver, lungs, kidneys, spleen, gastrointestinal tract, urinary bladder, and brain." Edema and necrotic changes were noted around the central veins of the liver. Cloudy swelling was noted in the kidneys along with changes in the cytoplasm of the cells lining the loop of Henle.

Repeated administration of sublethal doses produce no significant pathologic lesions.

GODFREY.

Lipschitz, W. L., and Stokey, E.: Diuretic Action of Formoguanamine in Normal Persons. J. Pharmacol. & Exper. Therap. 92:131 (Feb.), 1948.

The authors have previously reported the mode of diuretic action of formoguanamine (J. Pharmacol. & Exper. Therap. 83:235, 1945). Formoguanamine has been found to be markedly more effective as a diuretic than urea. Toxicity studies on dogs and rabbits failed to reveal any significant toxicity.

Formoguanamine was administered to eight healthy male volunteers in doses from 3.5 to 11.0 mg. per kilogram of body weight. Its diuretic action was compared with that of caffeine and theobromine. It was found to give a more consistant diuresis than either caffeine or theobromine. Both sodium chloride and water excretion were increased. No toxicity was noted in the eight volunteers.

GODFREY.

McNamara, B., Krop, S., and McKay, E. A.: The Effect of Calcium on the Cardiovascular Stimulation Produced by Acetylcholine. J. Pharmacol. & Exper. Therap. 92:153 (Feb.), 1948.

Acetylcholine causes a pressor response in animals that have been atropinized. This response, in turn, may be blocked by nicotine. The pressor response caused by acetylcholine is believed to be due to ganglionic stimulation and its blockage by nicotine to be due to ganglionic blockage.

The authors showed that by administering calcium they were able to inhibit the ganglionic blocking action of nicotine so that the acetylcholine effect was not abolished. This could be demonstrated in both the intact animal and the isolated heart. They also demonstrated that calcium potentiates the epinephrine effect upon the heart. They believe that aceltycholine acts directly upon the cardiac musculature by means of liberating an epinephrine-like substance. The fact that calcium potentiates epinephrine effects and also overcomes nicotine blockage sheds further light on its cardiac effects and the mechanism by which it acts upon the heart.

GODFREY.

Gore, I.: Myocardial Changes in Fatal Diphtheria. A Summary of Observations in 221 Cases. Am. J. M. Sc. 215:257 (March), 1948.

The author warns of certain ominous potentialities in connection with the incidence of diphtheria. Though there is a continuing downward trend in the United States since the practice of immunization became widespread, the disease has not been conquered, and the tremendously decreased carrier rate has been associated with a rising susceptibility, as indicated by the Schick test. Furthermore, the reduced exposure to diphtheria bacilli with the concurrent loss of its stimulating effect has contributed to the more rapid waning of artificially induced immunity. Such circumstances set the stage for a widespread reappearance of the disease should virulent organisms be introduced into the population. The present incidence of diphtheria in several of the European countries makes this possibility far from remote. It was, therefore, considered appropriate to report a study of that sequel of diphtheria which is most often lethal: myocarditis.

The study is based on a review of the autopsy records and slides of 221 fatal cases of diphtheria accumulated at the Army Institute of Pathology. Material from the heart was available for review in 205 of these. Myocarditis occurred in 143 (70 per cent). It was found that the longer the survival after the onset of diphtheria, the greater the incidence of this complication. Neuritis had a similar relationship to survival time, but it appeared still later and was less frequent. These two sequellae were not related causally to each other, and neither age nor color appeared to have any influence upon them.

Pathologically, the hearts were dilated, with flabby, pale, or mottled musculature, and frequently they were enlarged. Microscopically, there was a primary toxic degeneration of the fibers. The inflammatory response, which culminates in scarring, appeared to be secondary to the muscle injury.

In one-third of the cases the manifestations of myocarditis appeared at a time when the patient seemed to be well on his way to convalescence. The interval between diphtheria and the onset of cardiac symptoms has been designated the deceptive interval of apparent improvement. The importance of administration of antitoxin early and in adequate quantities is re-emphasized as a measure to prevent myocarditis (and neuritis). The designation of myocarditis as a sequel of the pharmacologic effect of the toxin rather than as an unexpected complication may contribute to the early and more frequent recognition of myocarditis.

A shock-like state following diphtheria must be recognized as a frequent manifestation of myocardial weakness lest the vigorous administration of intravenous fluids to combat it result in a fatal termination.

DURANT.

Slevin, J. G.: New Test in Diagnosis and Surgical Treatment of Varicose Veins. Am. J. Surg. 75:469 (March), 1948.

The author points out that there is considerable difference of opinion concerning the importance of incompetent communicating veins in the production of superficial varicose veins. Some workers believe that this type of vessel is rare and unimportant and that the reflux occurs

through the lesser saphenous vein. On the other hand, others, including the author, are of the opinion that incompetent communicating veins are the primary cause of recurrence after injection of a sclerosing solution, since backflow through the incompetent perforator either prevents a firm sclerosis or causes recanalization.

In order to determine the exact site of "blowouts," the author utilized the multiple tourniquet test. This is performed with the patient lying on the examining table with the lower extremity elevated until the superficial veins are empty. Tourniquets are then applied to the upper, middle, and lower thigh, and at least one is applied below the knee. When the patient stands, the tourniquets are removed from below upward within three to five seconds. A rapid filling of any segment before the highest tourniquet is removed indicates a Trendelenberg double positive reaction. The segment is noted and the test repeated so as to determine the exact location of the "blowout."

In the treatment of varicose veins, the author found sodium morrhuate to be the best sclerosing agent. Up to 4.0 c.c. of this solution is a safe amount to inject at one time if spread over two or more segments of the vein. By application of an elastic bandage to the leg for the first twenty-four hours after injection, less solution is needed and disfiguring knots in the leg are avoided. The author obtained effective cures in 96.6 per cent of his cases using high and low ligation technique, which permits the patient to return to work in two or three days. Vein stripping, as advocated by other workers, was found to be an unnecessary procedure in all but the exceptional case. ABRAMSON.

Cooper, W. M.: Treatment of Varicose Ulcer. Am. J. Surg. 75:475 (March), 1948.

The author precedes his discussion of the treatment of varicose ulcer with a section on the pathogenesis of this condition. He points out that the lesion is usually located in the region of the medial malleolus, the most distal point of the great saphenous system. In this site hydrostatic pressure and stagnation of fluid in the tissues are most marked in the presence of varicosities of the great saphenous vein. In addition, the exposed ankle is prone to minor trauma which frequently initiates the ulcer. The fact that the stagnant blood is oxygen poor and metabolite rich, when compared with blood removed from normal veins in the lower limb, is probably also important in reducing the resistance of the skin. Since superficial thrombophlebitis is a common occurrence in patients with long-standing varicose veins, the additional local phlebitis and lymphedema thus imposed upon an area of chronic stasis frequently act as the exciting factor in the production of the ulcer.

The author points out that once an ulcer starts, it almost invariably becomes infected. As a result, cellular infiltration occurs in the region of the margin and base of the ulcer and is followed by fibrosis and cicatrical contraction of the tissues. This latter reaction produces a reduction in local capillary and arteriolar blood supply.

With regard to treatment, the author is in favor of preliminary high ligation and division of the great saphenous vein, even before the ulcer is clean. It is his belief that the operation frequently shortens the period of pain and disability to a great extent. When dermatitis is present, resulting from stasis in the skin, bed rest for a short period of time, elevation of the extremity, and the application of Burow's solution, 1:20 strength, will usually clear up the condition. When considerable infection or epidermophytosis is present as a complicating factor, wet dressings of potassium permanganate 1:5,000 applied for a few days at the beginning of treatment are efficacious.

As soon as the skin clears and edema is reduced, ambulatory treatment is instituted. The author found that Daxalan, a proprietary substance composed of crude cold tar, zinc oxide, starch, and petrolatum as a base, was of considerable use in combatting local infection in the ulcer and stimulated healing. This ointment is applied to the ulcer after the skin has been cleansed, unscented talcum powder is sprinkled on the surface of the ointment, and a smooth, evenly applied Dome boot, a modified Unna's paste boot, is placed on the limb from the toes to the knee. The patient is instructed to return in one week. During this interval he is encouraged to be ambulant. After a week the boot is cut, the ulcer and surrounding skin cleansed with mineral oil, and a second application of Daxalan ointment, talcum powder, and Dome boot is made. This time the boot is allowed to remain on the limb for two weeks. The same routine is repeated until the ulcer is firmly healed.

The author has treated 147 subjects with chronic leg ulcers with this regimen and found the results wholly satisfactory as an ambulatory method of therapy. The maximal period of time required to effect a cure was ten weeks and the minimum, two weeks. Since two patients in the series were found to be sensitive to Daxalan, it is the author's opinion that a patch test should be done on each individual before beginning treatment, using an area of diseased skin. It is also necessary to avoid exposure to direct sunlight of the surface to which the ointment is applied or has recently been applied, since tar is a photosensitizer. Furthermore, prolonged use of the ointment on hairy areas may cause folliculitis. ABRAMSON.

Boger, W. P., Miller, A. K., Tillson, E. K., and Shaner, G. A.: Caronamide: Plasma Concentrations, Urinary Recoveries, and Dosage. J. Lab. & Clin. Med. 33:297 (March), 1948.

The purpose of this paper is to report the plasma concentration following various doses of Caronamide by the oral and parenteral route of administration, the amount recovered in the urine, and the correlation of simultaneously determined Caronamide and penicillin plasma concentration.

It was found that in order to obtain at least a two-fold elevation of penicillin plasma concentration, it was necessary to maintain a Caronamide plasma concentration of approximately 15 mg. per 100 cubic centimeters. A single oral dose of 4.0 Gm. of Caronamide will not maintain this concentration in the plasma but, by reason of partial inhibition of the renal tubules, will influence penicillin excretion from four to five hours. In some patients 1.5 Gm. of Caronamide every three hours raised the Caronamide plasma level to 15 mg. per 100 cubic centimeters. In the majority of patients, however, 3.0 Gm. every three hours or 4.0 Gm. every four hours were required in order to maintain critical levels. Caronamide plasma concentrations of 20 to 40 mg. per 100 c.c. are well tolerated and probably represent the concentrations that maximally inhibit the tubular excretion of penicillin. There are marked individual differences in the metabolism of this compound, but the average twenty-four hour recovery of free Caronamide is 35.8 per cent and of Caronamide and its metabolic products, 47.26 per cent of the material injected.

A simple and reliable method for Caronamide determination is described which permits the individualization of Caronamide dosage. KLINE.

Davison, S.: Spontaneous Rupture of a Papillary Muscle of the Heart. J. Mt. Sinai Hosp. 14:941 (March-April), 1948.

Spontaneous rupture of a papillary muscle of the heart is rare. Twenty cases were recorded in the literature up to 1935, and since that year six others have been reported. To this group three cases have been added by the author. One of these is the first recorded case where a clinical ante-mortem diagnosis was made.

In the great majority of the cases reviewed, spontaneous rupture of the papillary muscle was secondary to coronary artery occlusion and associated myocardial infarction. In several instances, however, thrombosis of a coronary artery was not demonstrated and arteriosclerosis of the coronary arterial tree was minimal. In this connection the concept of coronary insufficiency is pertinent. It has been shown that in coronary insufficiency the pathologic myocardial alterations are characteristic and consist mainly of focal or diffusely mottled or hemorrhagic areas in the subendocardial region of the left ventricle. The papillary muscles, particularly the posterior, show the predominant lesions. Furthermore, the papillary muscles do comparatively more work than other portions of the myocardium and react more readily to oxygen lack. These considerations suggest that coronary insufficiency may be the common denominator in instances of spontaneous papillary muscle rupture, with or without coronary artery occlusion.

The diagnosis of this cardiac catastrophe should be considered in any patient who has suffered a recent myocardial infarction accompanied by the development of a new murmur or with a change in the character and intensity of a murmur which antedated the infarction. The murmur is usually mitral in position, systolic in time, and becomes loud and harsh at the time of rupture. In addition there is usually a sudden radical change in the patient's condition, sudden death occurring not infrequently. This condition must be differentiated from a ruptured mitral chordae tendineae, rupture of an aortic cusp, and acute perforation of an infarcted interventricular septum. KLINE.

Cleland, W. P.: Cavernous Haemangioma of the Lung: Report of a Case. Thorax 3:48 (March), 1948.

The author reports the case of a woman, 51 years of age, who as a child had always been breathless and blue and was under constant observation for "heart trouble." Her father also had been similarly affected. She married while a young woman and had three children without undue difficulty. For several years preceding her death, her symptoms had become worse, and, in addition, she noticed undue fatigue, a winter cough associated with some sputum, and severe epistaxes recurring at almost weekly intervals. Six months before her demise she was admitted to the hospital where a diagnosis of pulmonary hemangioma with cardiac failure was made; the latter responded to rest and routine measures. She was later admitted for removal of the hemangioma of the lung. At this time the findings included intense cyanosis combined with multiple small hemangiomata on the face, eyelids, lips, buccal mucosa, nasal septum, base of the nails, and tongue. The heart was not clinically enlarged, and there were no cardiac murmurs. The blood pressure was 130/70. Over the base of the right lung there was a loud but fairly localized to-and-fro murmur, accompanied by a thrill. Angiocardiography showed the dye passing through a dilated right pulmonary artery into the lobulated tumor in the right lower lobe and back to the heart through a dilated pulmonary vein. It also demonstrated the vascular nature of the tumors in the left lung.

A lower lobectomy was performed without incident. Her general condition immediately after the operation was good. Some twelve hours after its conclusion, however, the pulse began to rise and the blood pressure to fall, and in spite of various measures her condition rapidly deteriorated and she died about twenty hours after the operation. Adequate cause of death was not found at autopsy.

KLINE.

Dontigny, P., Hay, E. C., Prado, J. L., and Selye, H.: Hormonal Hypertension and Nephrosclerosis as Influenced by the Diet. Am. J. M. Sc. 215:442 (April), 1948.

Previous work established the fact that treatment of rats with lyophilized anterior pituitary substance (LAP) leads, under certain experimental conditions, to characteristic renal and cardiovascular lesions which are similar to those produced by desoxycorticosterone acetate (DCA) or by various chronic, nonspecific stresses. The renal lesions are mainly characterized by enlargement and hyalinization of the glomeruli, formation of hyaline casts, dilatation of the renal tubules, and thickening and hyaline necrosis of arteriolar walls. These pathologic modifications are considered to be similar to those described in the malignant type of arterial hypertension, and are referred to as nephrosclerosis.

Various further studies of the factors involved in the LAP nephrosclerosis are presented in this report. It was found that a pronounced degree of hypertension occurs in a high percentage of the animals, but that this can be prevented (as well as the development of nephrosclerosis) by administration of a diet containing a minimum amount of protein (about 15 per cent). Five vitamins of the B group, including thiamin, riboflavin, pyridoxine, and calcium pantothenate, were inactive against the hypertension and nephrosclerosis, but choline chloride had a slight beneficial effect if given in excessive amounts (1.0 Gm. per 100 Gm. food). A very pronounced adrenal enlargement was always present in the hypertensive rats. Control animals on 15 per cent and 30 per cent casein diets showed no significant difference in adrenal weight, but in LAP-treated animals there was a very significant difference between adrenal weights in animals on low and high protein intakes.

Experiments now under way show that the hypertension produced by DCA is not influenced by diet in the same drastic manner as the LAP hypertension; animals receiving large doses of DCA develop nephrosclerosis and hypertension of almost equal intensity on diets containing 15 per cent or 30 per cent casein. This seems to indicate that the part played by the high-protein diet in the LAP hypertension results predominantly from the fact that it permits a pronounced enlargement of the suprarenal gland.

DURANT.

American Heart Association, Inc.

1775 Broadway, New York 19, N. Y.

Telephone Plaza 7-2045

GRANTS FOR RESEARCH IN CARDIOVASCULAR DISEASE BY THE AMERICAN HEART ASSOCIATION

The American Heart Association announces that applications for fellowships and for research in cardiovascular disease are available. Application blanks may be obtained by addressing Medical Director, American Heart Association, 1775 Broadway, New York 19, N. Y.

The ultimate aim of the American Heart Association is to develop a continuing program of productive research within the broad field of diseases of the heart and blood vessels.

The recommendations of the Research Policy Committee were published in the American Heart Journal 36: 463, September, 1948. These policies are subject to modification by the membership of the Scientific Council of the American Heart Association and approval by the Board of Directors.

The research program of the American Heart Association will be closely coordinated with that of the National Heart Institute of the National Institute of Health, United States Public Health Service and with the Life Insurance Medical Research Fund.

EXECUTIVE SECRETARIES OF LOCAL HEART ASSOCIATIONS HOLD FIRST NATIONAL CONFERENCE

The first National Conference of Executive Secretaries of local heart associations affiliated with the American Heart Association was held on October 19 and 20 at the Henry Hudson Hotel in New York City. Representatives of thirty-five local heart associations attended the conference.

Plans were discussed for the development of standards for cardiac clinics, employment and rehabilitation programs, educational methods and materials, local rheumatic fever programs, and community relationships.

Plans for cooperation of the newly created National Heart Institute of the United States Public Health Service with the program of the American Heart Association and its local affiliates were discussed by speakers representing both agencies.

A. W. Robertson, Chairman of the Board of the American Heart Association, presided at one session at which the fund-raising and publicity plans for the forthcoming campaign were reviewed. Speakers at the two-day meeting included Dr. H. M. Marvin, President-Elect of the American Heart Association; Dr. Charles A. R. Connor, Medical Director of the Association; Judson Hardy, Chief of the Office of Scientific Reports, National Institute of Health, United States Public Health Service; Lealon E. Martin, Jr., Chief, Heart Information Center, National Heart Institute.

WILLIAM E. COTTER EXECUTIVE VICE-CHAIRMAN OF 1949 NATIONAL CAMPAIGN

William E. Cotter, Counsel for the Union Carbide & Carbon Corp., New York, has been named Executive Vice-Chairman for the Association's 1949 National Campaign. Mr. Cotter will work with Harold E. Stassen, National Campaign Chairman, in directing the national campaign activities.

Mr. Cotter has held many executive positions in health and welfare organizations, including the American Red Cross, War Loan Drives, United China Relief, the USO, the National War Fund, New York University-Bellevue Medical Center Fund, the Lay Committee for Financing Medical Education, the Occupational Research Foundation, and the Greater New York Fund.

ADDITIONS TO NATIONAL CAMPAIGN COMMITTEES

Since the November issue of the American Heart Journal went to press with incomplete membership lists of the 1949 National Campaign Planning Committee and the National Sponsors Committee, the following have accepted membership:

SUPPLEMENTARY LIST

(Since September 28, 1948)

CAMPAIGN PLANNING COMMITTEE

Howard S. Cullman, Chairman
Port of New York Authority
New York

Juan T. Trippe, President
Pan American World Airways Corporation
New York

NATIONAL SPONSORS COMMITTEE

Charles Francis Adams, Chairman
State Street Trust Company
Boston

J. B. Adoue, Jr., President
National Bank of Commerce
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Charles Almy, Vice-President
Dewey & Almy Chemical Company
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Pepperell Manufacturing Company
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Consolidated Investment Trust
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George S. Armstrong & Company, Inc.
New York

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New York

Harry Bingham, President
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Henry P. Bristol, President
Bristol-Myers Company
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Brown Brothers Harriman & Company
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Rear Admiral Richard E. Byrd
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Curtis E. Calder, Chairman
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Honorable Charles G. Dawes, Chairman
City National Bank and Trust Company
Chicago

Donald W. Douglas
Douglas Aircraft Company, Inc.
Santa Monica, Calif.

Victor Emanuel, Chairman
Avco Manufacturing Corporation
New York

RESEARCH GRANTS AND FELLOWSHIPS TO BE MADE AVAILABLE IN 1949 BY THE LIFE INSURANCE MEDICAL RESEARCH FUND

Applications for grants in aid of research on cardiovascular problems to begin in 1949 will be received by the Life Insurance Medical Research Fund up to Jan. 15, 1949. Support is available for physiological, biochemical, and pathological research which bears on cardiovascular problems,

as well as for clinical investigation in this field. Preference is given to fundamental research. It is expected that about $500,000 will be awarded for these grants.

Applications for postgraduate fellowships for training in research in 1949 to 1950 will be received by this Fund up to January 1, 1949. Preference is given to candidates who wish to work in the broad field of cardiovascular function or disease and to candidates who wish to work in institutions other than those in which they have obtained most of their experience. A doctor's degree (M.D. or Ph.D.), or the equivalent, is required. The annual stipend varies, as a rule being between $2,500 and $3,500, with larger amounts in special cases. Approximately twelve fellowships will be available.

Later in the year, the Fund will also offer a number of student (pre-doctoral) research fellowships for 1949 to 1950.

Both grants and fellowships will become available on July 1, 1949.

Further information and application blanks may be secured from the Scientific Director, Life Insurance Medical Research Fund, 2 East 103rd Street, New York 29, N. Y.

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पंजीकृत समाचार पत्र
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